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(71) Applicant (*for all designated States except US*): **CELGENE CORPORATION** [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **MAN, Hon-Wah** [US/US]; 102 Bermuda Drive, Neshanic Station, NJ 08853 (US). **MULLER, George** [US/US]; 250 Windmill Court, Bridgewater, NJ 08807 (US).

(74) Agent: **KAKEFUDA, Mary, S.**; Mathews, Collins, Shepherd & Gould, P.A., Suite 306, 100 Thanet Circle, Princeton, NJ 08540 (US).

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(54) Title: PHARMACEUTICALLY ACTIVE ISOINDOLINE DERIVATIVES

(57) Abstract: Isoindolin-1-one and Isoindoline-1, 3-dione substituted in the 2-position with an α-(3, 4-disubstituted phenyl)alkyl group and in the 4- and/or 5-position with a nitrogen-containing group are inhibitors of, and thus useful in the treatment of disease states mediated by, TNFα and phosphodiesterase. A typical embodiment is 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione.

PHARMACEUTICALLY ACTIVE ISOINDOLINE DERIVATIVES

This is a continuation-in-part of U.S. Patent Application No. 09/590,344 filed June 8, 2000, which claims the benefit of U.S. Provisional Patent Application No. 60/165,168 filed November 12, 1999, the disclosures of which are incorporated by reference in their entirety.

The present invention pertains to non-polypeptide isoindoline derivatives that decrease the levels of tumor necrosis factor alpha (TNFα) and inhibit phosphodiesterases (PDEs), particularly PDE 4 and PDE 3, and to the treatment of disease states mediated thereby. The compounds inhibit angiogenesis and are useful in the treatment of cancer, inflammatory, and autoimmune diseases. For example, compounds that selectively inhibit PDE 4 are useful in treating inflammation and effecting relaxation of airway smooth muscle with a minimum of unwanted side effects, *e.g.*, cardiovascular or anti-platelet effects. The present invention also relates to methods of treatment and pharmaceutical compositions utilizing such compounds.

Background of the Invention

Tumor necrosis factor α, or TNFα, is a cytokine which is released primarily by mononuclear phagocytes in response to a number immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Excessive or unregulated TNFα production thus has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey *et al., Nature* 330, 662-664 (1987) and Hinshaw *et al., Circ. Shock 30,* 279-292 (1990)}; rheumatoid arthritis, Crohn's disease, IBD, cachexia {Dezube *et al., Lancet,* 335 (8690), 662 (1990)} and Adult Respiratory Distress Syndrome where TNFα concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from ARDS patients {Millar *et al., Lancet* 2(8665), 712-714 (1989)}. Systemic infusion

of recombinant TNFα also resulted in changes typically seen in ARDS {Ferrai-Baliviera *et al., Arch. Surg.* 124(12), 1400-1405 (1989)}.

TNFα appears to be involved in bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption, an activity to which the data suggest TNFα contributes. {Bertolini *et al., Nature* 319, 516-518 (1986) and Johnson *et al., Endocrinology* 124(3), 1424-1427 (1989)}. TNFα also has been shown to stimulate bone resorption and inhibit bone formation *in vitro and in vivo* through stimulation of osteoblast formation and activation combined with inhibition of osteoblast function. Although TNFα may be involved in many bone resorption diseases, including arthritis, a most compelling link with disease is the association between production of TNFα by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum TNFα levels have been associated with major complication following acute allogenic bone marrow transplants {Holler *et al., Blood,* 75(4), 1011-1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Levels of serum TNFα correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau *et al., N. Engl. J. Med.* 320(24), 1586-1591 (1989)}.

Unregulated angiogenesis is pathologic and sustains progression of many neoplastic and non-neoplastic diseases including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, *e.g.*, Moses *et al.*, 1991, *Biotech.* **9**:630-634; Folkman *et al.*, 1995, *N. Engl. J. Med.*, **333**:1757-1763; Auerbach *et al.*, 1985, *J. Microvasc. Res.* **29**:401-411; Folkman, 1985, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203; Patz, 1982, *Am. J. Opthalmol.* **94**:715-743; Folkman *et al.*, 1983, *Science* **221**:719-725; and

Folkman and Klagsbrun, 1987, *Science* 235:442-447. In addition, maintenance of the avascularity of the cornea, lens, and trabecular meshwork is crucial for vision as well as to cel lular physiology. See, *e.g.*, reviews by Waltman *et al.*, 1978, *Am. J. Ophthal.* **85**:704-710 and Gartner *et al.*, 1978, *Surv. Ophthal.* **22**:291-312.

Angiogenesis thus is encountered in various disease states, tumor metastasis, and abnormal growth by endothelial cells. Pathological states created by unregulated angiogenesis have been grouped together as angiogenic dependent or angiogenic associated diseases. Control of the angiogenic processes could lead to the mitigation of these conditions.

The components of angiogenesis relating to vascular endothelial cell proliferation, migration and invasion, have been found to be regulated in part by polypeptide growth factors. Endothelial cells exposed to a medium containing suitable growth factors can be induced to evoke some or all of the angiogenic responses. Polypeptides with *in vitro* endothelial growth promoting activity nclude acidic and basic fibroblast growth factors, transforming growth factors α and β, platelet-derived endothelial cell growth factor, granulocyte colony-stimulating factor, interleukin-8, hepatocyte growth factor, proliferin, vascular endothelial growth factor and placental growth factor. Folkman *et al.*, 1995, N. Engl. J. Med., 333:1757-1763.

Inhibitory influences predominate in the naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis. Rastinejad *et al.*, 1989, *Cell* 56:345-355. In those instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail.

Macrophage-induced angiogenesis is known to be mediated by TNFα. Leibovich *et al.* {*Nature*, 329, 630-632 (1987)} showed TNFα induces *in vivo* capillary blood vessel formation in the rat cornea and the developing chick chorioallantoic membranes at very low doses and suggest TNFα is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth.

TNFα production also has been independently associated with cancerous conditions, particularly induced tumors {Ching *et al., Brit. J. Cancer,* (1955) 72, 339-343, and Koch, *Progress in Medicinal Chemistry,* 22, 166-242 (1985)}. Whether or not involved with TNFα production, angiogenesis is prominent in solid tumor formation and metastasis and angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. Tumors in which angiogenesis is important include solid tumors, and benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas. Independent of its action on TNFα production, the prevention of angiogenesis could halt the growth of these tumors and the resultant damage to the animal due to the presence of the tumor. Angiogenesis has been associated with blood-born tumors such as leukemias and various acute or chronic neoplastic diseases of the bone marrow. In such conditions, unrestrained proliferation of white blood cells occurs, usually accompanied by anemia, impaired blood clotting, and enlargement of the lymph nodes, liver, and spleen.

Angiogenesis also is involved in tumor metastasis. Thus angiogenesis stimulation occurs in vascularization of the tumor, allowing tumor cells to enter the blood stream and circulate throughout the body. After the tumor cells have left the primary site, and have settled into the secondary, metastasis site, angiogenesis must occur before the new tumor can grow and expand.

All of the various cell types of the body can be transformed into benign or malignant tumor cells. The most frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, including brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, and head and neck cancer.

TNFα also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNFα completely blocked the silica-induced lung fibrosis in mice {Pignet *et al., Nature,* 344:245-247 (1990)}. High levels of TNFα production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette *et al., Inflammation* 13(3), 329-339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNFα as compared with macrophages from normal donors {Baughman *et al., J. Lab. Clin. Med.* 115(l), 36-42 (1990)}.

TNFα is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder *et al., PNAS* 87, 2643-2646 (1990)}. TNFα also alters the properties of endothelial cells and has various procoagulant activities, such as producing an increase in tissue factor procoagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry *et al., J. Cell Biol.* 107, 1269-1277 (1988)}. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNFα-induced expres-

sion of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro *et al., Am. J Path.* 135(I), 121-132 (1989)}.

TNFα blockage with monoclonal anti-TNFα antibodies has been shown to be beneficial in rheumatoid arthritis {Elliot *et al., Int. J. Pharmac.* 1995 17(2), 141-145} and Crohn's disease {von Dullemen *et al., Gastroenterology,* 1995 109(I), 129-135}

Moreover, it now is known that TNFα is a potent activator of retrovirus replication including activation of HIV-1. {Duh *et al., Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll *et al., Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto *et al., Blood* 79, 2670 (1990); Clouse *et al., J. Immunol.* 142, 431-438 (1989); Poll *et al., AIDS Res. Hum. Retrovirus,* 191-197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified; *i.e.*, HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNFα, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNFα, in an HIV-infected individual assists in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg *et al., The Immunopathogenesis of HIV Infection,* Advances in Immunology, 57 (1989)}. Cytokines, such as TNFα, have been shown to activate HIV replication in monocytes and/or macrophages {Poli *et al., Proc. Natl. Acad. Sci.,* 87, 782-784 (1990)}; therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNFα as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osbom, *et al., PNAS* 86 2336-2340). This evidence suggests that a reduction of TNFα synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNFα {Folks *et al., PNAS* 86, 2365-2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNFα's ability to activate a gene regulatory protein (NFκB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osbom *et al., PNAS* 86, 2336-2340 (1989)}. TNFα in AIDS associated cachexia is suggested by elevated serum TNFα and high levels of spontaneous TNFα production in peripheral blood monocytes from patients {Wright *et al., J. Immunol.* 141(I), 99-104 (1988)}. TNFα has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

The nuclear factor κB (NFκB) is a pleiotropic transcriptional activator (Lenardo, *et al., Cell* 1989, 58, 227-29). NFκB has been implicated as a

transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNFα and also to be an activator of HIV transcription (Dbaibo, *et al.*, *J Biol. Chem.* 1993, 17762-66; Duh *et al.*, *Proc. Natl. Acad. Sci.* 1989, 86, 5974-78; Bachelerie *et al.*, *Nature* 1991, 350, 709-12; Boswas *et al.*, *J Acquired Immune Deficiency Syndrome* 1993, 6, 778-786; Suzuki *et al.*, *Biochem. And Biophys. Res. Comm.* 1993, 193, 277-83; Suzuki *et al.*, *Biochem. And Biophys. Res. Comm.* 1992, 189, 1709-15; Suzuki *et al.*, *Biochem. Mol. Bio. Int.* 1993, 31(4), 693-700; Shakhov *et al.*, *Proc. Natl. Acad. Sci. USA* 1990, 171, 35-47; and Staal *et al.*, *Proc. Natl. Acad. Sci. USA* 1990, 87, 9943-47). Thus, inhibition of NFκB binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds described herein can inhibit the action of NFκB in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, cancer, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, inflammatory bowel disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS. TNFα and NFκB levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNFα and NFκB.

Many cellular functions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). Such cellular functions can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory media-

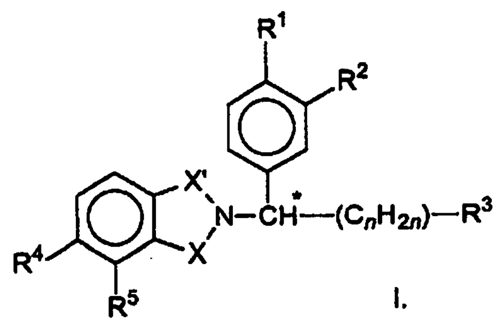
tors, including TNFα and NFκB. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE) (Beavo and Reitsnyder, *Trends in Pharm.*, **11**, 150-155, 1990). There are seven known members of the family of PDEs. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle (Verghese, et al., *Journal of Pharmacology and Experimental Therapeutics*, **272(3)**, 1313-1320, 1995). Thus, compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects. Currently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses. The compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of disease states mediated thereby.

Decreasing TNFα levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury.

Detailed Description

The present invention pertains to compounds of Formula I in which the carbon atom designated * constitutes a center of chirality:



I.

In Formula I, each of R^1 and R^2, independently of the other, is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, cycloalkoxy of 3 to 18 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or cycloalkylmethoxy in which cycloalkyl has from 3 to 18 carbon atoms, one of X and X' is =C=O or $=SO_2$ and the other of X and X' is a divalent group selected from =C=O, $=CH_2$, $=SO_2$ or $=CH_2C=O$,

n has a value of 1, 2, or 3;

R^3 is $-SO_2-Y$, -COZ, -CN , or hydroxyalkyl of 1 to 6 carbon atoms in which

Y is alkyl of 1 to 6 carbon atoms, phenyl, or benzyl,

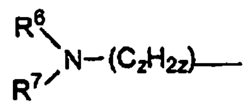
Z is $-NR^{6'}R^{7'}$, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl,

$R^{6'}$ is hydrogen, alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, or alkylamino of 1 to 4 carbon atoms, and

$R^{7'}$ is hydrogen or alkyl of 1 to 4 carbon atoms,

R^4 and R^5, when taken together, are -NH-CH$_2$-R^8-, -NH-CO-R^8- or -N=CH-R^8- in which -R^8- is -CH$_2$-, -O-, -NH-, -CH=CH-, -CH=N-, or -N=CH-.

Alternatively, when taken independently of each other, one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, pyrrolyl; oxadiazolyl, triazolyl, or



in which

z is 0 or 1,

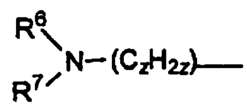
R^6, when taken independently of R^7, is hydrogen; alkyl of 1 to 4 carbon atoms,cycloalkyl of 3 to 18 carbon atoms, alkanoyl of 2 to 5 carbon atoms, or cycloalkanoyl of 2 to 6 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; alkoxyalkylcarbonyl of 2 to 5 carbon atoms; N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; or methylsulfonyl; and

R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, or methylsufonyl, or alkoxyalkylcarbonyl of 2 to 5 carbon atoms.

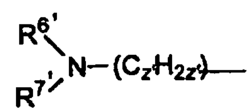
Prerrably z is not 0 when (*i*) R^3 is -SO$_2$-Y-COZ, or -CN and (*ii*) R^4 or R^5 is hydrogen.

When taken together, R^6 and R^7 can be -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms.

In addition, one of R^4 and R^5 is:



in which each of R^6, R^7, and z is as just define and the other of R^4 and R^5 is:



in which z' is 0 or 1; $R^{6'}$ has the same meaning as, but is selected independently of, R^6; and $R^{7'}$ has the same meaning as, but is selected independently of, R^7.

The present invention also pertains to the acid addition salts of these isoindoline derivatives which are susceptible of protonation. Such salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

The compounds preferrably are administered as a substantially chirally pure isomer, (S)- or (R)-, but can also be dministered as a mixture of the (S)-isomer and the (R)-isomer.

The compounds can be prepared through a number of methods. Often it is advantageous to utilized protected groups including but not limited to functional groups convertible to the desired group. For example, the reactions described herein can be performed with intermediates in which either or both of R^4 and R^5 are nitro groups with the nitro group(s) then being catalytically reduced (hydrogenated) to an amine or diamine, as the case may be. Similarly, one can employ an intermediate in which either or both of R^4 and R^5 is a cyano group and the final compound can then be reduced to yield the corresponding aminomethyl compound. Likewise, the carbonyl comprised by R^3 can be processed in the form of a secondary alcohol which is thereafter is oxidized to the carbonyl compound, utilizing for example pyridinium chlorochromate.

Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed or converted to the desired group at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol.15/I, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

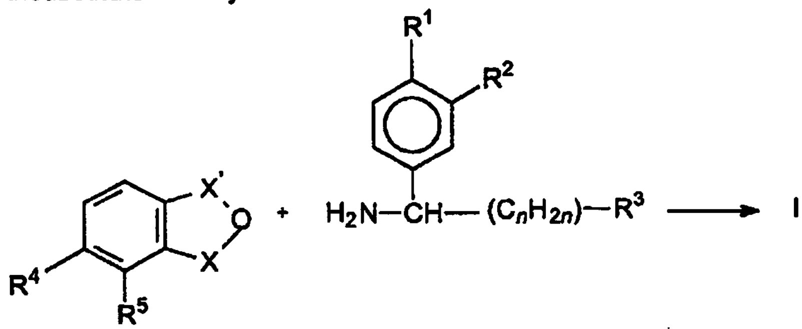
An amino group thus can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially formyl, a lower alkanoyl group which is branched in 1- or α position to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, or a lower alkanoyl group which is substituted in the position α to the carbonyl group, as for example trifluoroacetyl.

Should a carboxy group require protection, it can be converted to an ester which is selectively removable under sufficiently mild conditions not to disrupt the desired structure of the molecule, especially a lower alkyl ester of 1 to 12 carbon atoms such as methyl or ethyl and particularly one which is branched at the 1- or α position such as t-butyl; and such lower alkyl ester substituted in the 1- or 2-position with (*i*) lower alkoxy, such as for example, methoxymethyl, 1-methoxyethyl, and ethoxymethyl, (*ii*) lower alkylthio, such as for example methylthiomethyl and 1-ethylthioethyl; (*iii*) halogen, such as 2,2,2-trichloroethyl, 2-bromoethyl, and 2-iodoethoxycarbonyl; (*iv*) one or two phenyl groups each of which can be unsubstituted or mono-, di- or tri-substituted with, for example lower alkyl such as tert.-butyl, lower alkoxy such as methoxy, hydroxy, halo such as chloro, and nitro, such as for example, benzyl, 4-nitrobenzyl, diphenylmethyl, di-(4-methoxyphenyl)-methyl; or (*v*) aroyl, such as phenacyl. A carboxy group also can be protected in the form of an organic silyl group such as trimethylsilylethyl or tri-lower alkylsilyl, as for example tri-methylsilyloxycarbonyl.

Many, but not all, of the compounds described herein proceed through compounds in which either or both of R^4 and R^5 are amino or a protected amino group. The amino group is then further processed as hereinafter described. One can also employ a starting material in which R^4 and/or R^5 is an amide; *e.g.*,4-acetamidophthalic acid or 2-chloroacetamide. The product of the latter reaction then can be allowed to react with sodium

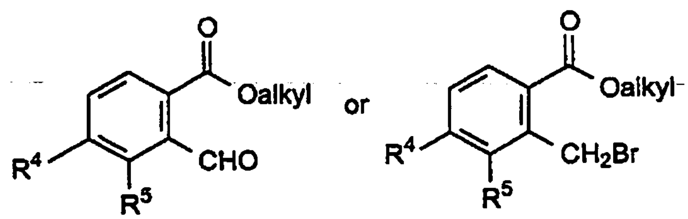
azide followed by triphenylphosphine to yield a 2-amino-N-substituted acetamide.

In one embodiment, an anhydride or lactone is allowed to react with an α,3,4-trisubstituted benzylamine:



In the above, at least one of X and X' is =C=O. One also can employ the diacid, *e.g.*, an R^4, R^5 disubstituted phthallic acid, and remove the water formed. Activated derivative thereof also can be employed.

The compounds in which X is $=CH_2$ can be prepared from the same trisubstituted benzylamine and a formyl or bromomethyl benzoate derivative:



Analogously, an R^4,R^5 benzene *ortho* dialdehyde can be allowed to react with the above α,3,4-trisubstituted benzylamine in the form of the ammonium chloride salt.

The foregoing reactions also can be performed with compound in which R^4 and R^5 form a heterocylic ring. For example, using furano[3,4-h]quinoline-1,3-dione in place of phthallic acid anhydride, the corresponding 2-substituted pyrrolino[3,4-h]quinoline-1,3-dione is obtained.

When in formula I R^4 and R^5 are both amino, the compound can be further reacted. Using dimethylformamide dimethyl acetal, for example, yields a pyrrolino[3,4-e]benzimidazole; *i.e.*, R^4 and R^5 together are -N=CH-NH-. The corresponding hydropyrrolino[3,4-e]benzimidazole can be obtained from the diamine and triphosgene whereas if one instead employs the diamine and glyoxal, the product is the corresponding 3-pyrrolino[3,4-f]quinoxaline.

In the case of only one of R^4 and R^5 in formula I being amine, the same can be reacted with an appropriate acid halide or anhydride to yield the corresponding amide. The same reaction can be conducted using chloroformate to yield the methoxycarboxamide derivative.

If the amide is formed from the amine and chloroacetyl chloride, *i.e.*, producing a chloroacetamide derivative, this can be followed by treatment with ammonia or a primary or secondary amine to yield the corresponding aminoacetamide; *e.g.*, treatment with dimethylamine produces the corresponding dimethylaminoacetamide. A compound in which either or both of R^4 and R^5 is amino also can be subjected to reductive formylation to form the corresponding N,N-dimethylamino compound.

A compound in which either or both of R^4 and R^5 is amino also can be reacted with dimethylformamide dimethyl acetal to yield the corresponding 1-aza-2-(dimethylamino)vinyl compound.

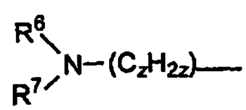
Compounds in which one of R^4 and R^5 is a heterocyclic group can be prepared in number of ways. An isoindoline 4- or 5-carboxylic acid can be reacted with carbonyldiimidazole followed by acetic hydrazide to yield the corresponding 4-(5-methyl-1,3,4-oxadiazol-2-yl)isoindoline or 5-(5-methyl-1,3,4-oxadiazol-2-yl)isoindoline. Alternatively, a mono amine and 2,5-dimethoxytetrahydrofuran are allowed to react to yield 4- or 5-pyrrolylisoindoline. Similarly a 4-aminomethyl or 5-aminomethyl (prepared

as described above) and dimethoxytetrahydrofuran are allowed to react to yield the corresponding pyrrolylmethyl compound.

A first preferred subgroup are those compounds of Formula I in which R^4 and R^5 together are $-NH-CH_2-R^8-$, $-NH-CO-R^8-$ or $-N=CH-R^8-$ in which $-R^8-$ is $-CH_2-$, -O-, -NH-, -CH=CH-, -CH=N-, or -N=CH-. It will be appreciated that each of the chains that is not symmetrical can be arranged in either of two orientations, each of which is within the scope of this invention.

A second preferred subgroup are those compounds of Formula I in which one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, oxadiazolyl, pyrrolyl, or triazolyl.

A third preferred subgroup are those compounds of Formula I in which one of R^4 and R^5 is:

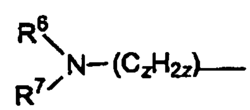


in which *z* is 0 or 1; R^6 when taken independently of R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, N-alkylaminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; aminoalkanoyl of 2 to 5 carbon atoms, N-alkylaminoalkanoyl of 2 to 5 carbon atoms, phenyl, benzyl, or methylsulfonyl; and R^7 is hydrogen or alkyl of 1 to 4 carbon atoms, or R^6 and R^7 taken together are -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, al-

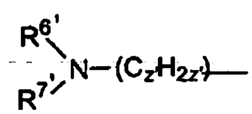
kylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms.

Within this third preferred subgroup, a first further preferred subgroup are compounds in which R^6 is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, or benzyl. A second further preferred subgroup are compounds in which R^6 is alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and R^7 is hydrogen.

A fourth preferred subgroup are those compounds of Formula I in which one of R^4 and R^5 is:



and the other of R^4 and R^5 is



in which each of z and z' independently is 0 or 1; R^6 has the meaning given above, $R^{6'}$ has the same meaning as, but is selected independently of, R^6; R^7 has the meaning given above, and $R^{7'}$ has the same meaning as, but is selected independently of, R^7.

Within this fourth preferred subgroup, a first further preferred subgroup are compounds in which each of R^6 and $R^{6'}$, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, or benzyl. A second further

preferred subgroup are compounds in which each of R^6 and $R^{6'}$, independently of the other, is alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and each of R^7 and $R^{7'}$ is hydrogen.

A third further preferred subgroup are compounds in which one of R^6 and $R^{6'}$ is alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and the other of R^6 and $R^{6'}$ is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, or benzyl; and each of R^7 and $R^{7'}$ is hydrogen.

Additional preferred subgroups for all of the above are compounds in which one of X and X' is =C=O, and the other is =C=O, $=CH_2$, or $=SO_2$. and compounds in which each of R^1 and R^2, independently of the other, is methyl, ethyl, *n*-propyl, *i*-propyl, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclopentyl, cyclohexyl, cycloheptyl, or cyclopropylmethoxy.

The compounds possess a center of chirality and thus can exist as optical isomers. Both the chirally pure (R)- and (S)-isomers as well as mixtures (including but not limited to racemic mixtures) of these isomers, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. Mixtures can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, or have such as the individual enantiomers of 10-

camphorsulfonic acid, camphoric acid, bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; *i.e.*, in a form having an optical purity of >95%.

Inhibition of PDE III, PDE IV, TNFα and NFκB by these compounds can be conveniently assayed using methods known in the art, *e.g.*, enzyme immunoassay, radioimmunoassay, immunoelectrophoresis, affinity labeling, etc., of which the following are typical.

PBMC from normal donors are obtained by Ficoll-Hypaque density centrifugation. Cells are cultured in RPMI supplemented with 10% AB+ serum, 2mM L-glutamine, 100 U/mL penicillin and 100 mg/mL streptomycin.

The test compounds are dissolved in dimethylsulfoxide (Sigma Chemical), further dilutions are done in supplemented RPMI. The final dimethylsulfoxide concentration in the presence or absence of drug in the PBMC suspensions is 0.25 wt %. The test compounds are assayed at half-log dilutions starting at 50 mg/mL. The test compounds are added to PBMC (10^6 cells/mL) in 96 wells plates one hour before the addition of LPS.

PBMC (10^6 cells/mL) in the presence or absence of test compound are stimulated by treatment with 1 mg/mL of LPS from *Salmonella minnesota* R595 (List Biological Labs, Campbell, CA). Cells are then incubated at 37°C for 18-20 hours. Supernatants areharvested and assayed immediately for TNFα levels or kept frozen at -70°C (for not more than 4 days) until assayed.

The concentration of TNFα in the supernatant is determined by human TNFα ELISA kits (ENDOGEN, Boston, MA) according to the manufacturer's directions.

Phosphodiesterase can be determined in conventional models. For example, using the method of Hill and Mitchell, U937 cells of the human

promonocytic cell line are grown to $1x10^6$ cells /mL and collected by centrifugation. A cell pellet of $1x10^9$ cells is washed in phosphate buffered saline and then frozen at -70°C for later purification or immediately lysed in cold homogenization buffer (20mM Tris-HCl, pH 7.1, 3 mM 2-mercaptoethanol, 1 mM magnesium chloride, 0.1 mM ethylene glycol-*bis*-(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), 1 μM phenylmethylsulfonyl fluoride (PMSF), and 1 μg/mL leupeptin). Cells are homogenized with 20 strokes in a Dounce homogenizer and supernatant containing the cytosolic fraction are obtained by centrifugation. The supernatant then is loaded onto a Sephacryl S-200 column equilibrated in homogenization buffer. Phosphodiesterase is eluted in homogenization buffer at a rate of approximately 0.5 mL/min and fractions are assayed for phosphodiesterase activity -/+ rolipram. Fractions containing phosphodiesterase activity (rolipram sensitive) are pooled and aliquoted for later use.

The phosphodiesterase assay is carried out in a total volume of 100 μl containing various concentration of test compounds, 50mM Tris-HCl, pH 7.5, 5 mM magnesium chloride, and 1 μM cAMP of which 1% was ^3H cAMP. Reactions are incubated at 30°C for 30 minutes and terminated by boiling for 2 minutes. The amount of phosphodiesterase IV containing extract used for these experiments is predetermined such that reactions are within the linear range and consumed less than 15% of the total substrate. Following termination of reaction, samples are chilled at 4°C and then treated with 10μl 10 mg/mL snake venom for 15 min at 30°C. Unused substrate then is removed by adding 200μl of a quaternary ammonium ion exchange resin (AG1-X8, BioRad) for 15 minutes. Samples then are spun at 3000 rpm, 5 min and 50 μl of the aqueous phase are taken for counting. Each data point is carried out in duplicate and activity is expressed as percentage of control. The IC_{50} of the compound then is determined from dose response curves of a minimum of three independent experiments.

The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα, NFκB, and phosphodiesterase. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, *etc.*, to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20-100 milligrams/milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1000 milligrams/day as needed in single or multiple daily administration. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNFα activity for other TNFα mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of cytokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is observed following the normal treatment regimen, then the amount of cytokine activity interfering agent administered is increased, *e.g.*, by fifty percent a week.

The compounds of the present invention can also be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNFα production, such as viral infections, for example those caused by the herpes viruses or viral conjunctivitis, psoriasis, other skin disorders and diseases, *etc.*

The compounds can also be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNFα production. TNFα mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

The invention thus includes various methods of treatment including the method of inhibiting PDE IV, the method of reducing or inhibiting undesirable levels of TNFα, method of reducing or inhibiting undesirable levels of matrix metalloproteinases, the method of treating undesirable angiogenesis, the method of treating cancer, the method of treating inflammatory disease, the method of treating autoimmune disease, the method of treating arthritis, the method of treating rheumatoid arthritis, the method of treating inflammatory bowel disease, the method of treating Crohn's disease, the method of treating aphthous ulcers, the method of treating cachexia, the method of treating graft versus host disease, the method of treating asthma, the method of treating adult respiratory distress syndrome, and the method of treating acquired immune deficiency syndrome, by administering to a mammalan an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound of Formula I or a mixture of those isomers. While these methods may overlap, they also may differ in terms of method of administration, dose level, dosage regimen (such as single or multiple doses), and concurrently administered therapeutic agents.

The invention also includes pharmaceutical compositions in which (*i*) a quantity of a substantially chirally pure (R)- or (S)-isomer of a compound of Formula I or a mixture of those isomers, that upon administration in a single or multiple dose regimen is pharmaceutically effective is combined with (*ii*) a pharmaceutically acceptable carrier .

Pharmaceutical compositions can be typified by oral dosage forms that include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Mixtures containing from 20 to 100 mg/mL can be formulated for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions will comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple

dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

EXAMPLE 1

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-dinitroisoindoline-1,3-dione

A mixture of 3,4-dinitrophthalic acid (4.63 g, 18.1 mmol) and 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulfonyl)eth-2-ylamine (4.94 g, 18.1 g) in toluene (70 mL) was heated to reflux for 15 hours. The water was removed by a Dean-Stark trap. To the reaction mixture was added ethyl acetate (150 mL). The organic layer was extracted with water, sodium hydrogen carbonate (sat), brine (100 mL each), and dried over magnesium sulfate. The solvent was removed in vacuo to give a solid. The solid was recrystallized from ethanol (300 mL) to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-dinitroisoindoline-1,3-dione as an orange solid (4.35 g, 49% yield): mp, 122.0-124.0° C; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 6.9 Hz, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.65 (dd, J = 3.9, 14.3 Hz, 1H, CHH), 3.86 (s, 3H, CH_3), 4.10 (q, J = 6.9 Hz, 2H, CH_2), 4.56 (dd, J = 11.4, 14.1 Hz, 1H, CHH), 5.90 (dd, J = 3.9, 11.1 Hz, 1H, NCH), 6.84 (d, J = 8.0 Hz, 1H, Ar), 7.07-7.11 (m, 2H, Ar), 8.16 (d, J = 8.2 Hz, 1H, Ar), 8.60 (d, J = 7.9 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.66, 41.66, 49.57, 53.38, 55.98, 64.61, 111.61, 112.42, 120.64, 123.93, 126.18, 127.85, 131.93, 136.74, 138.10, 142.45, 148.77, 150.17, 161.57, 163.47; Anal Calcd for $C_{20}H_{19}N_3O_{10}S$ +

0.1 ethyl acetate: C, 48.78; H, 3.97; N, 8.37. Found: C, 48.50; H, 3.77; N, 8.07. (HNMR showed the sample contained ~10% eq of ethyl acetate).

EXAMPLE 2

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-dinitroisoindoline-1,3-dione (4.35 g, 8.81 mmol) and Pd/C (800 mg) in ethyl acetate (200 mL) was shaken under hydrogen (50-60 psi) in a Parr bottle for 16 hours. The suspension was filtered through a pad of Celite filter material. The Celite filter material was washed with acetone (200 mL). The solvent was removed in vacuo to give a solid. The solid was stirred in ethyl acetate (10 mL) for 2 hours. The suspension was filtered to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione as a yellow solid (2.79 g, 73% yield): mp, 205-207° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.95-4.07 (m, 3H, CHH), 4.37 (dd, J = 10.4, 14.0 Hz, 1H, CHH), 5.67 (dd, J = 3.9, 10.2 Hz, 1H, NCH), 5.90-6.00 (m, 4H, 2NH_2), 6.64 (d, J = 7.7 Hz, 1H, Ar), 6.88-6.92 (m, 3H, Ar), 7.06 (s, 1H, Ar); ^{13}C NMR (CDCl$_3$) δ 14.64, 40.94, 46.65, 53.53, 55.46, 63.79, 109.36, 111.74, 112.29, 114.42, 117.04, 119.55, 130.68, 133.98, 134.06, 142.38, 147.74, 148.63, 167.16, 169.38; Anal Calcd for $C_{20}H_{23}N_3O_6S$: C, 55.42; H, 5.35; N, 9.69. Found: C, 55.71; H, 5.30; N, 9.29. MS: 434 (M^++1), 456 (M^++23 Na).

EXAMPLE 3

7-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-e]benzimidazole-6,8-dione

To a solution of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione (310 mg, 0.72 mmol) in acetic acid (5 mL) was added dimethylformamide dimethyl acetal (3 mL). The solution was heated to reflux for 17 hours. The solvent was removed in vacuo to give an oil. The oil was stirred in sodium hydrogen carbonate (50 mL, sat.) and

ethyl acetate (100 mL). The organic layer was separated, washed with brine (50 mL), and dried over magnesium sulfate. The solvent was removed in vacuo to give an oil. The oil was separated by chromatography (silica gel, 7:13:0.5 methylene chloride:ethyl acetate:MeOH) to give 7-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-e]benzimidazole-6,8-dione as a white solid (220 mg, 69% yield): mp, 143-145° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 3.02 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.02 (q, J = 6.9 Hz, 2H, CH_2), 4.15 (dd, J = 4.3, 14.3 Hz, 1H, CHH), 4.40 (dd, J = 10.5, 14.3 Hz, 1H, CHH), 5.81 (dd, J = 4.3, 10.4 Hz, 1H, NCH), 6.92-7.01 (m, 2H, Ar), 7.12 (s, 1H, Ar), 7.67 (d, J = 8.2 Hz, 1H, Ar), 8.02 (d, J = 8.0 Hz, 1H, Ar), 8.62 (s, 1H, CH), 13.49 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 14.64, 41.02, 47.17, 53.24, 55.46, 63.81, 111.78, 112.33, 116.34, 119.67, 125.84, 129.98, 147.64, 147.85, 148.79, 166.63, 168.23; Anal Calcd for $C_{21}H_{21}N_3O_6S$: C, 54.23; H, 5.07; N, 9.03. Found: C, 54.13; H, 4.65; N, 8.76; MS: 444 (M^{+}+1), 466 (M^{+}+23 Na).

EXAMPLE 4

7-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]hydro-3-pyrrolino[3,4-e]benzimidazole-2,6,8-trione

To a solution of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione (600 mg, 1.38 mmol) in methylene chloride (1 mL) was added triphosgene (0.43 g, 1.4 mmol) at room temperature and kept for 30 minutes. To the mixture was added sodium hydrogen carbonate (50 mL, sat.) and ethyl acetate (80 mL). The organic layer was washed with brine (50 mL) and dried over magnesium sulfate. The solvent was removed in vacuo to give a solid. The solid was then recrystallized from ethanol to give 7-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]hydro-3-pyrrolino[3,4-e]benzimidazole-2,6,8-trione as a brown solid (390 mg, 62% yield). mp, 242-244° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 3.01 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.01 (q, J = 6.9 Hz, 2H, CH_2), 4.11 (dd, J = 4.3, 14.3 Hz, 1H, CHH), 4.37 (dd, J =

10.7, 14.3 Hz, 1H, CH*H*), 5.76 (dd, *J* = 4.1, 10.3 Hz, 1H, NC*H*), 6.91-6.92 (m, 2H, Ar), 7.08 (s, 1H, Ar), 7.23 (d, *J* = 7.7 Hz, 1H, Ar), 7.45 (d, *J* = 7.8 Hz, 1H, Ar), 11.47 (s, 1H, N*H*), 11.87 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.64, 41.01, 47.07, 53.14, 55.46, 63.83, 110.41, 111.78, 112.00, 112.37 116.72, 119.67, 122.79, 125.76, 129.96, 136.29, 147.81, 148.80, 155.86, 166.11, 167.59; Anal Calcd for $C_{21}H_{21}N_3O_7S$ + 1.1 H_2O: C, 52.63; H, 4.88; N, 8.77; H_2O, 4.13. Found: C, 52.48; H, 4.73; N, 8.53; H_2O, 4.07.

EXAMPLE 5

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-h]quinoline-1,3-dione

A mixture of 2-(3-ethoxy-4-methoxyphenyl)-1-(methylsulfonyl)eth-2-ylamine (0.69 g, 2.5 mmol), furano[3,4-h]quinoline-1,3-dione (0.50 g, 2.5 mmol) and sodium acetate (0.25 g, 3.1 mmol) in acetic acid (10 mL) was heated to reflux for 18 hours. The solvent was removed in vacuo to give an oil. The resulting oil was stirred in ether/hexane/water (30/5/30 mL) for 18 hours. The suspension was filtered to give a solid. The solid was stirred in hot methanol. The suspension was filtered to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-h]quinoline-1,3-dione as an off-white solid (0.8 g, 70% yield): mp, 223-225° C; ^{1}H NMR ($CDCl_3$); δ 1.47 (t, *J* = 6.8 Hz, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.79-3.86 (m, 1H, CH*H*), 3.84 (s, 3H, CH_3), 4.12 (q, *J* = 6.9 Hz, 2H, CH_2), 4.63 (dd, *J* = 10.4, 14.3 Hz, 1H, CH*H*), 5.98 (dd, *J* = 4.5, 10.3 Hz, 1H, NC*H*), 6.82-6.85 (m, 1H, Ar), 7.19-7.22 (m, 2H, Ar), 7.57 (dd, *J* = 4.2, 8.4 Hz, 1H, Ar), 7.95 (t, *J* = 8.2 Hz, 1H, Ar), 8.17 (d, *J* = 8.3 Hz, 1H, Ar), 8.27 (dd, *J* = 1.4, 8.4 Hz, 1H, Ar), 9.24 (dd, *J* = 1.7, 4.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.61, 41.36, 48.90, 54.73, 55.88, 64.47, 11.41, 112.57, 119.55, 120.55, 123.20, 126.89, 129.48, 132.19, 134.43, 135.69, 136.68, 142.79, 148.55, 149.59, 154.30, 167.11, 167.62; Anal Calcd for $C_{23}H_{22}N_2O_6S$: C, 60.78; H, 4.88; N, 6.16. Found: C, 60.57; H, 4.79; N, 5.95.

EXAMPLE 6

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-f]quinoxaline-1,3-dione

To a solution of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione (433 mg, 1.0 mmol) in tetrahydrofuran (2 mL) was added glyoxal (0.15 mL, 1.3 mmol). The solution was heated to reflux for 7 hours. To the suspension was added ether (10 mL). The suspension was filtered and washed with ether to give an orange solid. The solid was stirred in ethanol (20 mL) for 18 hours. The suspension was filtered and washed with ethanol to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-f]quinoxaline-1,3-dione as an orange solid (200 mg, 44% yield): mp, 122.0-124.0° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 3.03 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.03 (q, J = 6.9 Hz, 2H, CH_2), 4.20 (dd, J = 4.5, 14.4 Hz, 1H, CHH), 4.39 (dd, J = 10.5, 14.1 Hz, 1H, CHH), 5.87 (dd, J = 4.5, 10.2 Hz, 1H, NCH), 6.92-6.96 (m, 1H, Ar), 7.03-7.07 (m, 1H, Ar), 7.15 (d, J = 1.7 Hz, 1H, Ar), 8.23 (d, J = 8.4 Hz, 1H, Ar), 8.53 (d, J = 8.4 Hz, 1H, Ar), 9.14 (d, J = 1.7 Hz, 1H, Ar), 9.22 (d, J = 1.7 Hz, 1H, Ar); ^{13}C NMR (DMSO-d6) δ 14.63, 41.05, 47.49, 53.07, 55.47, 63.81, 111.73, 112.41, 119.80, 122.66, 126.93, 129.48, 134.08, 137.06, 137.25, 145.02, 147.87, 147.93, 148.87, 148.96, 165.37, 167.05; Anal Calcd for $C_{22}H_{21}N_3O_6S$ + 0.2 H_2O: C, 57.56; H, 4.70; N, 9.15; H_2O, 0.78. Found: C, 57.34; H, 4.70; N, 9.15; H_2O, 0.41.

EXAMPLE 7

Cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}carboxamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (570 mg, 1.4 mmol) and cyclopropane carbonyl chloride (2 mL) was heated to reflux for 15 minutes. To the mixture was added methanol (20 mL) and water (5 mL) at room temperature and kept for 30 minutes. The solvent was removed in vacuo to give an oil. The oil

was stirred in ether/hexane (15 mL each) for 1 hour to give a suspension. The suspension was filtered and washed with ether to give a yellow solid. The solid was then stirred in ethanol (10 mL) overnight. The suspension was filtered and washed with ethanol to give cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}carboxamide as a yellow solid (380 mg, 57.4% yield); mp, 153-155° C; ^1H NMR ($CDCl_3$) δ 0.92-0.99 (m, 2H, 2CH*H*), 1.11-1.17 (m, 2H, 2CH*H*), 1.48 (t, J = 6.9 Hz, 3H, CH_3), 1.61-1.71 (m, 1H, C*H*), 2.88 (s, 3H, CH_3), 3.75 (dd, J = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, CH_3), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 4.57 (dd, J = 10.4, 14.3 Hz, 1H, CH*H*), 5.89 (dd, J = 4.4, 10.3 Hz, 1H, NC*H*), 6.84-6.88 (m, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.48 (d, J = 7.2 Hz, 1H, Ar), 7.65 (t, J = 7.4 Hz, 1H, Ar), 8.76 (d, J = 8.5 Hz, 1H, Ar), 9.69 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.71, 14.62, 16.16, 41.58, 48.59, 54.60, 55.89, 64.50, 111.49, 112.44, 114.83, 117.91, 120.26, 124.99, 129.27, 130.99, 136.02, 137.77, 148.63, 149.76, 167.49, 169.52, 172.79; Anal Calcd for $C_{24}H_{26}N_2O_7S$: C, 59.25; H, 5.39; N, 5.76. Found: C, 59.06; H, 5.30; N, 5.69.

EXAMPLE 8

2-Chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (2.0 g, 4.8 mmol) and chloroacetyl chloride (2 mL, 25 mmol) was heated to reflux for 30 minutes. The solvent was removed in vacuo to give a solid. The solid was stirred in ether (40 mL) for 1 hour to give a suspension. The suspension was filtered and washed with ether to give 2-chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid (2.28 g, 96% yield); mp, 166-168° C; ^1H NMR ($CDCl_3$) δ 1.48 (t, J = 6.9 Hz, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.75 (dd, J = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, CH_3), 4.13 (q, J = 7.0 Hz, 2H, CH_2), 4.24 (s, 2H, CH_2), 4.57 (dd, J =

10.5, 14.3 Hz, 1H, CH*H*), 5.89 (dd, *J* = 4.5, 10.3 Hz, 1H, NC*H*), 6.84-6.88 (m, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.57 (d, *J* = 7.2 Hz, 1H, Ar), 7.70 (t, *J* = 7.6 Hz, 1H, Ar), 8.77 (d, *J* = 8.3 Hz, 1H, Ar), 10.53 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.60, 41.52, 42.67, 48.72, 54.51, 55.88, 64.48, 111.46, 112.44, 116.37, 119.06, 120.38, 124.74, 129.17, 131.22, 136.04, 136.29, 148.58, 149.75, 165.21, 167.25, 169.01; Anal Calcd for $C_{22}H_{23}N_2O_7ClS$ + 0.1 H_2O: C, 53.19; H, 4.71; N, 5.50; H_2O, 0.36. Found: C, 52.89; H, 4.52; N, 5.50; H_2O, 0.17.

EXAMPLE 9

2-Amino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of 2-chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide (0.30 g, 0.61 mmol) and sodium azide (90 mg, 1.38 mmol) in acetone (10 mL) was heated to reflux for 8 hours. To the solution was added triphenylphosphine (0.30 g, 1.1 mmol) and water (0.4 mL). The solution was heated to reflux for 5 more h. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (10 mL) and water (10 mL) overnight to give a suspension. The suspension was filtered and washed with ether and water to give 2-amino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide as a yellow solid (250 mg, 86% yield); mp, 111-112° C; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.74 (brs, 2H, N*H*$_2$), 2.86 (s, 3H, C*H*$_3$), 3.57 (s, 2H, C*H*$_2$), 3.77 (dd, *J* = 4.6, 14.5 Hz, 1H, CH*H*), 3.86 (s, 3H, C*H*$_3$), 4.11 (q, *J* = 7.0 Hz, 2H, C*H*$_2$), 4.56 (dd, *J* = 10.2, 14.2 Hz, 1H, CH*H*), 5.89 (dd, *J* = 4.6, 10.2 Hz, 1H, NC*H*), 6.82-6.85 (m, 1H, Ar), 7.12-7.15 (m, 2H, Ar), 7.52 (d, *J* = 7.2 Hz, 1H, Ar), 7.67 (t, *J* = 7.5 Hz, 1H, Ar), 8.86 (d, *J* = 8.3 Hz, 1H, Ar), 11.21 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.68, 41.51, 48.65, 54.69, 55.88, 64.49, 111.45, 112.50, 115.81, 118.24, 120.37, 124.94, 129.38, 131.29, 135.90, 136.88, 148.55, 149.68, 167.64,

168.83, 172.41; Anal Calcd for $C_{22}H_{25}N_3O_7S$: C, 55.57; H, 5.30; N, 8.84. Found: C, 55.46; H, 5.33; N, 8.35.

EXAMPLE 10

2-N,N-Dimethylamino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide HCl

A mixture of 2-azido-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide (0.80 g, 1.59 mmol), Pd/C (0.2 g) and formaldehyde (10 mL, 37% wt in water) in ethanol (90 mL) was shaken under hydrogen (50-60 psi) in a Parr flask for 3 days. The suspension was filtered through a pad of Celite and washed with acetone (50 mL). The solvent was removed in vacuo to give an oil. The oil was stirred in methanol (10 mL). The suspension was filtered and washed with methanol to give a white solid. To the solid in ethyl acetate (20 mL) was added hydrogen chloride in ether (1.5 mL, 1N) to give a suspension. The suspension was filtered and washed with ether to give 2-N,N-dimethylamino-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}acetamide hydrogen chloride as a yellow solid (300 mg, 35% yield); mp, 105-107° C; ^{1}H NMR (DMSO-d6) δ 1.33 (t, J = 6.9 Hz, 3H, CH_3), 2.87 (s, 6H, 2CH_3), 3.03 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 4.02 (q, J = 7.0 Hz, 2H, CH_2), 4.16 (dd, J = 4.2, 14.3 Hz, 1H, CH*H*) 4.25 (brs, 2H, CH_2), 4.34 (dd, J = 10.8, 14.4 Hz, 1H, CH*H*), 5.79 (dd, J = 4.2, 10.4 Hz, 1H, NC*H*), 6.92-6.99 (m, 2H, Ar), 7.08 (s, 1H, Ar), 7.69 (d, J = 7.3 Hz, 1H, Ar), 7.88 (t, J = 7.7 Hz, 1H, Ar), 8.21-8.27 (m, 1H, Ar), 10.29 (s, 1H, *H*Cl), 10.64 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.65, 41.04, 43.36, 47.23, 52.86, 55.51, 58.09, 63.86, 111.79, 112.39, 119.22, 119.68, 127.78, 127.99, 129.42, 131.76, 134.25, 134.34, 135.95, 147.87, 148.92, 164.60, 166.79; Anal Calcd for $C_{24}H_{29}N_3O_7S$ + 1.1 HCl + 0.3 H_2O: C, 52.50; H, 5.64; N, 7.65; Cl, 7.10. Found: C, 52.16; H, 5.75; N, 7.37; Cl, 7.20.

EXAMPLE 11

N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}-2,2,2-trifluoroacetamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (1.0 g, 2.4 mmol) and trifluoroacetic anhydride (3 mL) was heated to reflux for 30 minutes. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (5 mL) and hexane (40 mL) for 3 days. The suspension was filtered and washed with ether to give a yellow solid. The solid was then recrystallized from ethanol (10 mL) to give N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}-2,2,2-trifluoroacetamide as a yellow solid (280 mg, 23% yield): mp, 130-132° C; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 6.9 Hz, 3H, CH_3), 2.92 (s, 3H, CH_3), 3.70 (dd, J = 4.2, 14.3 Hz, 1H, CH*H*), 3.87 (s, 3H, CH_3), 4.13 (q, J = 6.9 Hz, 2H, CH_2), 4.59 (dd, J = 10.9, 14.3 Hz, 1H, CH*H*), 5.90 (dd, J = 4.2, 10.9 Hz, 1H, NC*H*), 6.86 (d, J = 8.3 Hz, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.66 (d, J = 7.2 Hz, 1H, Ar), 7.77 (t, J = 7.5 Hz, 1H, Ar), 8.70 (d, J = 8.4 Hz, 1H, Ar), 10.39 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.59, 41.57, 48.68, 54.10, 55.89, 64.50, 111.48, 112.38, 115.16 (q, J_{CF} = 286 Hz), 117.19, 120.28, 120.31, 125.01, 128.85, 131.26, 134.63, 136.35, 148.63, 149.85, 155.36 (q, J^2_{CF} = 38 Hz), 166.78, 169.14; Anal Calcd for $C_{22}H_{21}N_2O_7F_3S$: C, 51.36; H, 4.11; N, 5.44. Found: C, 51.20; H, 4.07; N, 5.20.

EXAMPLE 12

N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindolin-4-yl}methoxycarboxamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (0.70 g, 1.7 mmol) and methyl chloroformate (25 mL) was heated to reflux for 30 minutes. To the mixture was added ethanol (5 mL). The suspension was filtered and washed with ethanol to give N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-

dioxoisoindolin-4-yl}methoxycarboxamide as a white solid (0.48 g, 60% yield): mp, 178-180° C; ^1H NMR ($CDCl_3$); δ 1.48 (t, J = 7.1 Hz, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.76 (dd, J = 4.4, 14.4 Hz, 1H, CH*H*), 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.12 (q, J = 6.9 Hz, 2H, CH_2), 4.55 (dd, J = 10.3, 14.4 Hz, 1H, CH*H*), 5.87 (dd, J = 4.5, 10.3 Hz, 1H, NC*H*), 6.83-6.87 (m, 1H, Ar), 7.09-7.13 (m, 2H, Ar), 7.45 (d, J = 7.0 Hz, 1H, Ar), 7.66 (t, J = 8.3 Hz, 1H, Ar), 8.50 (d, J = 8.5 Hz, 1H, Ar), 8.93 (brs, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.61, 41.52, 48.62, 52.70, 54.58, 55.88, 64.46, 111.40, 112.39, 114.78, 117.42, 120.29, 123.43, 129.27, 131.22, 135.97, 137.74, 148.59, 149.69, 153.42, 167.35, 169.23; Anal Calcd for $C_{22}H_{24}N_2O_8S$: C, 55.45; H, 5.08; N, 5.88. Found: C, 55.32; H, 5.00; N, 5.73.

EXAMPLE 13

4-[1-Aza-2-(dimethylamino)vinyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (1.5 g, 3.6 mmol) and dimethylformamide dimethyl acetal (4 mL) was heated to reflux for 30 minutes. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (20 mL). The suspension was filtered and washed with ether to give 4-[1-aza-2-(dimethylamino)vinyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione as a yellow solid (1.1 g, 65% yield): mp, 161-163° C; ^1H NMR ($CDCl_3$) δ 1.46 (t, J = 6.9 Hz, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.11-3.12 (2s, 6H, 2CH_3), 3.82 (dd, J = 5.2, 14.5 Hz, 1H, CH*H*), 3.85 (s, 3H, CH_3), 4.10 (q, J = 6.9 Hz, 2H, CH_2), 4.49 (dd, J = 9.5, 14.6 Hz, 1H, CH*H*), 5.86 (dd, J = 5.2, 9.4 Hz, 1H, NC*H*), 6.80-6.83 (m, 1H, Ar), 7.11-7.19 (m, 3H, Ar), 7.39-7.52 (m, 2H, Ar), 7.72 (s, 1H, C*H*); ^{13}C NMR ($CDCl_3$) δ 14.68, 34.49, 40.41, 41.49, 48.78, 55.45, 55.93, 64.47, 111.41, 111.65, 116.99, 118.98, 120.54, 129.99, 130.58, 133.16, 134.49, 148.48, 149.50, 152.06, 156.64, 168.06, 168.19; Anal Calcd for

$C_{23}H_{27}N_3O_6S$: C, 58.34; H, 5.75; N, 8.87. Found: C, 58.17; H, 5.71; N, 8.69.

EXAMPLE 14

4-[1-Aza-2-(dimethylamino)prop-1-enyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (1.5 g, 3.6 mmol) and dimethylacetamide dimethyl acetal (4 mL) was heated to reflux for 30 minutes. The solvent was removed in vacuo to give an oil. The oil was stirred in ether/hexane/ethyl acetate (10/10/1 mL) overnight. The suspension was filtered to give an orange solid. The solid was separated by chromatography (Silica gel, 1% methanol in methylene chloride) to give 4-[1-aza-2-(dimethylamino)prop-1-enyl]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione as a yellow solid (140 mg, 8% yield): mp, 111-113° C; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J = 6.9 Hz, 3H, CH_3), 1.87 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.79 (dd, J = 4.9, 14.6 Hz, 1H, CH*H*), 3.87 (s, 3H, CH_3), 4.10 (q, J = 6.9 Hz, 2H, CH_2), 4.50 (dd, J = 9.8, 14.6 Hz, 1H, CH*H*), 5.84 (dd, J = 4.9, 9.7 Hz, 1H, NC*H*), 6.80-6.83 (m, 2H, Ar), 7.20 (d, J = 8.3 Hz, 1H, Ar), 7.10-7.12 (m, 2H, Ar), 7.36 (d, J = 7.1 Hz, 1H, Ar), 7.49 (t, J = 7.6 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.61, 15.59, 38.06, 41.36, 48.51, 55.25, 55.86, 64.41, 111.36, 112.56, 116.20, 118.78, 120.36, 129.98, 131.24, 132.67, 134.36, 148.41, 149.42, 150.80, 158.65, 167.78, 168.27; Anal Calcd for $C_{24}H_{29}N_3O_6S$: C, 59.12; H, 6.00; N, 8.62. Found: C, 58.84; H, 6.01; N, 8.36.

EXAMPLE 15

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(5-methyl-1,3,4-oxadiazol-2-yl)isoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindoline-4-carboxylic acid (1.5 g, 3.4 mmol) and carbonyldiimidazole (600 mg, 3.7 mmol) in tetrahydrofuran (10 mL) was stirred at room

temperature for 2 hours. To the mixture was added acetic hydrazide (411 mg, 5.54 mmol) and kept for 16 h. The mixture was extracted with ethyl acetate (125 mL) and water (40 mL). The organic layer was washed with sodium hydrogen carbonate (50 mL, sat), and dried over magnesium sulfate. The solvent was removed in vacuo to give a yellow solid (0.8 g). The solid and phosphoryl trichloride (2 mL) in acetonitrile (20 mL) was heated to reflux for 15 hours. To the mixture was added water (10 mL) then sodium hydrogen carbonate (60 mL, sat) until pH ~8. The aqueous layer was extracted with ethyl acetate (150 mL). The organic layer was washed with sodium hydrogen carbonate (50 mL, sat), brine (50 mL) and dried over magnesium sulfate. The solvent was removed in vacuo to give a yellow solid. The solid was separated by chromatography (silica gel, 50:50 ethyl acetate/methylene chloride) to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(5-methyl-1,3,4-oxadiazol-2-yl)isoindoline-1,3-dione as a yellow solid (450 mg, 28% yield): mp, 99-101° C; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 6.9 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.78 (dd, J = 4.6, 14.5 Hz, 1H, CHH), 3.86 (s, 3H, CH_3), 4.11 (q, J = 6.9 Hz, 2H, CH_2), 4.57 (dd, J = 10.3, 14.3 Hz, 1H, CHH), 5.94 (dd, J = 4.6, 10.2 Hz, 1H, NCH), 6.83-6.86 (m, 1H, Ar), 7.12-7.16 (m, 2H, Ar), 7.86 (t, J = 7.8 Hz, 1H, Ar), 8.04 (dd, J = 0.8, 7.2 Hz, 1H, Ar), 8.28 (dd, J = 1.0, 7.9 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.14, 14.60, 41.49, 48.95,54.51, 55.8, 64.48, 111.43, 112.49, 120.49, 121.49, 125.95, 128.43, 129.09, 133.11, 134.36, 135.26, 148.58, 149.74, 161.94, 164.99, 165.07, 166.69; Anal Calcd for $C_{23}H_{23}N_3O_7S$ + 0.6 ethyl acetate: C, 56.67; H, 5.20; N, 7.80. Found: C, 56.29; H, 4.82; N, 7.97.

EXAMPLE 16

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-pyrrolylisoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (1.0 g, 2.4 mmol) and 2,5-dimethoxytetrahydro-

furan (0.33 mL, 2.5 mmol) in acetic acid (1 mL) was heated to reflux for 2 hours. The solvent was removed in vacuo to give a yellow solid. The solid was stirred in ethanol (25 mL) for 1 hour. The suspension was filtered and washed with ethanol to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-pyrrolylisoindoline-1,3-dione as a brown solid (1.12 g, 100 % yield): mp, 95-97° C; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 6.9 Hz, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.73 (dd, J = 4.5, 14.4 Hz, 1H, CH*H*), 3.86 (s, 3H, CH_3), 4.11 (q, J = 6.9 Hz, 2H, CH_2), 4.60 (dd, J = 10.6, 14.4 Hz, 1H, CH*H*), 5.91 (dd, J = 4.4, 10.4 Hz, 1H, NC*H*), 6.39-6.41 (m, 2H, Ar), 6.84 (d, J = 8.0 Hz, 1H, Ar), 7.12-7.17 (m, 4H, Ar), 7.60-7.65 (m, 1H, Ar), 7.74-7.78 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.60, 41.44, 48.77, 54.32, 55.88, 64.48, 110.74, 111.41, 112.57, 120.52, 120.99, 122.00, 129.25, 130.09, 133.74, 135.36, 138.62, 148.52, 149.67, 165.77, 166.82; Anal Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16; N, 5.98. Found: C, 61.34; H, 5.17; N, 5.83.

EXAMPLE 17

4-(Aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-isoindoline-1,3-dione hydrochloride

A mixture of 4-cyano-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione (0.5 g, 1.17 mmol) and 10%Pd/C (0.15 g) in 4 N hydrochloric acid (1 mL) and methanol (40 mL) was hydrogenated in Parr Shaker apparatus under 50 psi of hydrogen overnight. To the resulting slurry was added water (2 mL) to dissolve the product. The reaction mixture was then filtered through Celite and the filtrate was concentrated in vacuo. The residue was slurried in ethyl acetate (10 mL) to afford 0.52 g of the crude product. The product was reslurried in hot ethanol (15 mL) to afford 4-(aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione hydrochloride (0.44 g, 80% yield): mp 237-239° C; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 3H, Ar), 8.04-7.89 (m, 3H, Ar), 7.11-6.91 (m, 3H, Ar), 5.83-5.77 (dd, J = 4.2, 10.1 Hz, 1H, NC*H*), 4.49-4.47 (m, 2H, CH_2), 4.41-4.31 (m, 1H, CH*H*), 4.21-4.13 (m, 1H, CH*H*), 4.04 (q, J = 6.8 Hz,

2H, CH_2), 3.73 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 1.32 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 167.48, 166.93, 148.95, 147.87, 135.39, 134.71, 132.82, 131.32, 129.50, 128.30, 123.34, 119.89, 112.55, 111.79, 63.87, 55.52, 53.07, 47.46, 41.08, 36.84, 14.66; Anal. Calcd for $C_{21}H_{25}N_2O_6SCl$: C, 53.79; H, 5.37; N, 5.97; S, 6.84; Cl, 7.56. Found: C, 53.49, H, 5.47; N, 5.75; S, 6.61; Cl, 7.51.

EXAMPLE 18

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione

A mixture of 4-(aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione (0.34 g, 0.79 mmol) and 2,5-dimethoxytetrahydrofuran (0.10 g, 0.79 mmol) in acetic acid (5 mL) was heated to reflux for 1 hour. The reaction mixture was then concentrated in vacuo and the residue was stirred with ethyl acetate (50 mL) and saturated sodium bicarbonate (25 mL). The organic layer was washed with water (25 mL), brine (25 mL), dried and concentrated. The residue was purified by flash chromatography (methylene chloride:ethyl acetate, 95:5) to afford 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione (0.23 g, 60% yield): mp 80-82° C; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 7.3 Hz, 1H, Ar), 7.57 (t, J = 7.7 Hz, 1H, Ar), 7.26 (m, 2H, Ar), 7.15 (d, J = 7.0 Hz, 2H, Ar), 6.96 (d, J = 7.8 Hz, 1H, Ar), 6.71 (d, J = 1.7 Hz, 1H, Ar), 6.22 (d, J = 1.8 Hz, 1H, Ar), 5.94-5.88 (dd, J = 4.4 and 10.3 Hz, 1H, NCH), 5.57 (s, 2H, CH_2), 4.63-4.53 (dd, J = 10.7, 14.4 Hz, 1H, CHH), 4.13 (q, J = 7.0 Hz, 2H, CH_2), 3.85 (s, 3H, CH_3), 3.80-3.72 (dd, J = 4.4,14.4 Hz, 1H, CHH), 2.86 (s, 3H, CH_3), 1.47 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.08, 167.69, 149.72, 148.63, 138.71, 134.74, 132.65, 131.86, 129.44, 126.92, 122.69, 121.46, 120.47, 112.49, 111.44, 109.15, 64.51, 55.95, 54.65, 48.73, 48.57, 41.58, 14.69; Anal. Calcd for $C_{25}H_{26}N_2O_6S$: C, 62.23; H, 5.43; N, 5.81; S, 6.64. Found: C, 62.25; H, 5.56; N, 5.63; S, 6.83.

EXAMPLE 19

3-(tert-Butyloxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)propionic Acid

A mixture of 3-amino-3-(ethoxy-4-methoxyphenyl)propionic acid (20 g, 83.5 mmol), 2N sodium hydroxide (50 mL), t-butanol (42 mL) and water (80 mL) was stirred at 10° C. Di-(*tert*-butyl)dicarbonate (20 g, 91.6 mmol) was added in portions over 25 minutes. The resulting mixture was stirred at room temperature for 2 hours (maintained at pH 10 by the addition of 2N sodium hydroxide). The mixture was washed with ether and the aqueous solution was acidified to pH 2 with 6N hydrochloric acid. The slurry was filtered and washed with water to yield 3-(tert-butyloxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)propionic acid as a white solid (28.3 g, 100%); ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 6.86-6.78 (m, 3H), 5.83 (d, J=8.3 Hz, 1H), 4.98 (b, 1H), 4.09 (q, J=7.0 Hz, 2H), 3.83 (s, 3H), 2.77 (m, 2H), 1.46-1.41 (m, 12H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 173.22, 155.02, 148.15, 147.89, 134.31, 117.97, 111.22, 111.07, 79.12, 64.01, 55.09, 50.76, 40.78, 28.11, 14.55.

EXAMPLE 20

3-(tert-Butyloxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-N-methylpropanamide

A mixture of carbonyldiimidazole (0.96 g, 5.9 mmol), 3-(tert-butoxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)propionic acid (2.0 g, 5.9 mmol) and methylene chloride (25 mL) was stirred at room temperature for 1 hr and then cooled to 5° C. A solution of N,O-dimethylhydroxyamine hydrochloride (0.86 g, 8.85 mmol) and 1-methylpiperidine (0.87 g, 8.85 mmol) in methylene chloride (10 mL) was added slowly. The mixture was stirred at room temperature for 1 hr and then quenched with water (20 mL). The organic layer was separated and then was washed with 1N citric acid, water, and brine. The organic layer was dried and concentrated *in vacuo* to give an oil. This oil was purified by chromatography (silica gel, methylene

chloride:ethyl acetate 8:2) to afford 3-(tert-butyloxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-N-methylpropanamide as a white solid (1.76 g, 78%); ^{1}H NMR ($CDCl_3$) δ 6.86-6.78 (m, 3H), 6.07 (b, 1H), 5.01 (m, 1H), 4.10 (q, J=6.9 Hz, 2H), 3.84 (s, 3H), 3.50 (s, 3H), 3.10 (s, 3H), 3.02 (m, 2H), 2.84-2.75 (dd, J=5.3 and 15.2 Hz, 1H), 1.45 (t, J=7.1 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.81, 155.18, 148.39, 148.19, 134.82, 118.12, 111.41, 111.18, 79.27, 64.26, 61.19, 55.90, 51.25, 37.80, 31.87, 28.33, 14.73.

EXAMPLE 21

(tert-Butoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]carboxamide

Methyl magnessium bromide (3M, 19.6 mL, 58.8 mmol) was slowly added to a stirred solution of 3-(tert-butyloxycarbonylamino)-3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-N-methylpropanamide (9.0 g, 23.5 mmol) in tetrahydrofuran (80 mL) at 5-12° C. After the addition was complete, the mixture was stirred at room temperature for 1.5 hours. The mixture was then cooled to 5° C, quenched with sat. ammonium chloride (40 mL) and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with 1N citric acid, sat. sodium bicarbonate, H_2O, brine, dried, and then concentrated to yield an oil. The oil was purified by chromatography (silica gel, methylene chloride:ethyl acetate 9:1) to give (tert-bytoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]carboxamide as a white solid (6.4 g, 81%); mp 118-120° C; ^{1}H NMR ($CDCl_3$) δ 6.83-6.80 (m, 3H), 5.30 (b, 1H), 5.01-4.99 (m, 1H), 4.10 (q, J=6.9 Hz, 2H), 3.84 (s, 3H), 2.99-2.85 (m, 2H), 2.09 (s, 3H), 1.48-1.41 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 206.98, 155.07, 148.61, 148.32, 118.15, 117.47, 111.36, 79.65, 64.34, 55.93, 50.99, 49.42, 30.58, 28.31, 14.25; Anal. Calcd. For $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.90; H, 8.13; N, 3.97.

EXAMPLE 22

(tert-Butoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]carboxamide

A mixture of (tert-butoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]carboxamide (2.0 g, 5.92 mmol) and sodium borohydride (0.4 g, 12.0 mmol) in methanol (40 mL) and tetrahydrofuran (10 mL) was stirred at -10 to -20° C for 4 hours. The mixture was quenched with water (10 mL) and then concentrated in vacuo to afford an oil. The oil was dissolved in ethyl acetate and washed with water, brine, dried, and concentrated in vacuo to afford an oil. The oil was purified by chromatography (silica gel, methylene chloride:ethyl acetate 8:2) to give the two diasteromers of (tert-butoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl)carboxamide:

A; 0.98 g (49%); ^{1}H NMR ($CDCl_3$) δ 6.83-6.81 (m, 3H), 4.99-4.96 (m, 1H), 4.85-4.83 (m, 1H), 4.11 (q, J=6.9 Hz, 2H), 3.85 (s, 3H), 3.78 (m, 1H), 1.80-1.75 (m, 2H), 1.49-1.45 (m, 12H), 1.24 (d, J=6.1 Hz, 3H).

B; 0.84 g (42%); ^{1}H NMR ($CDCl_3$) δ 6.82 (m, 3H), 5.06-5.03 (m, 1H), 4.68 (m, 1H), 4.11 (q, J=7.0 Hz, 2H), 3.85 (s, 3H), 3.82-3.70 (m, 1H), 1.94-1.82 (m, 2H), 1.48-1.40 (m, 12H), 1.21 (d, J=6.2 Hz, 3H).

EXAMPLE 23

4-Amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol Hydrochloride

A mixture of (tert-butoxy)-N-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]carboxamide (0.98 g, 2.89 mmol) and 4Nhydrochloric acid/dioxane (3 mL) in methylene chloride (10 mL) was stirred at room temperature for 16 hours. The resulting slurry was filtered and washed with ethyl acetate to give 4-amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol hydrochloride as a white solid (0.68 g, 85%); ^{1}H NMR (D_2O) δ 7.12 (m, 3H), 4.47 (t, J=7.0 Hz, 1H), 4.20 (q, J=7.4 Hz, 2H), 3.90 (s, 3H), 3.83-3.76 (m, 1H), 2.21-2.15 (m, 2H), 1.43 (t, J=6.9 Hz, 3H), 1.24 (d, J=6.1 Hz, 3H); ^{13}C NMR (D_2O) δ 151.75, 150.48, 131.92, 123.09, 115.05, 114.54, 67.86, 66.98, 58.53, 55.35, 44.41, 24.49, 16.68.

EXAMPLE 24

N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of 4-amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol hydrochloride (0.5 g, 1.81 mmol), 3-acetamidophthalic anhydride (0.37 g, 1.81 mmol) and triethylamine (0.18 g, 1.81 mmol) in dimethylformamide (10 mL) was heated at 80-90° C for 7 hours. The mixture was concentrated in vacuo to an oil. The oil was dissolved in ethyl acetate, washed with water, brine, dried, filtered and concentrated to an oil. This oil was purified by chromatography (silica gel, methylene chloride/ethyl acetate 8:2) to give N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid (0.5 g, 65%); mp 132-134° C; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H), 8.73 (d, J=8.4 Hz, 1H), 7.62 (t, J=7.4 Hz, 1H), 7.46 d, J=7.3 Hz, 1H), 7.12-7.08 (m, 2H), 6.83 (d, J=8.0 Hz, 1H), 5.46 (t, J=7.8 Hz, 1H), 4.12 (q, J=7.1 Hz, 2H), 3.84 (s, 3H), 3.80 (m, 1H), 2.59-2.42 (m, 2H), 2.25 (s, 3H), 1.65 (s, 1H), 1.45 (t, J=7.0 Hz, 3H), 1.27 (d, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.36, 169.20, 167.96, 149.04, 148.26, 137.29, 135.70, 131.50, 131.35, 124.60, 120.61, 117.85, 113.10, 111.25, 66.00, 64.39, 55.89, 52.43, 40.19, 24.92, 24.33, 14.73; Anal. Calcd. For $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15; N, 6.57. Found: C, 64.86; H, 6.10; N, 6.46.

EXAMPLE 25

N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.2 g, 2.81 mmol), pyridium chlorochromate (1.21 g, 5.63 mmol) and celite (0.6 g) in methylene chloride (35 mL) was stirred at room temperature for 4 hours. The mixture was filtered through celite and the celite washed with methylene chloride. The filtrate was washed with water, brine, dried, and concentrated. The residue was purified by chromatography (silica gel, methylene chloride:ethyl acetate 9:1) to

yield N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid (0.9 g, 76%); mp 128-129° C; ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 8.71 (d, J=8.4 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.46 (d, J=7.2 Hz, 1H), 7.06-7.03 (m, 2H), 6.82 (d, J=8.9 Hz, 1H), 5.73-5.07 (dd, J=5.2 and 10.0 Hz, 1H), 4.11 (q, J=7.0 Hz, 2H), 4.04-3.93 (dd, J=10.0 and 18.0 Hz, 1H), 3.83 (s, 3H), 3.28-3.19 (dd, J=5.2 and 18.0 Hz, 1H), 2.26 (s, 3H), 2.18 (s, 3H), 1.46 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.18, 170.62, 169.17, 167.10, 149.21, 148.40, 137.38, 135.81, 131.34, 131.24, 124.69, 120.02, 117.91, 115.30, 112.57, 111.37, 64.44, 55.93, 49.96, 44.82, 30.14, 24.93, 14.73; Anal. Calcd. For $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.11; H, 5.64; N, 6.50.

EXAMPLE 26

N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of R-4-amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol (1.5 g, 5.44 mmol), 3-acetamidophthalic anhydride (1.11 g, 5.44 mmol) and triethylamine (0.55 g, 5.44 mmol) was heated at 80-90° C for 7 hours. The mixture was concentrated in vacuo to an oil. The oil was dissolved in ethyl acetate and washed with water, brine, dried and concentrated. The residue was purified by chromatograhpy (silica gel, methylene chloride:ethyl acetate 8:2) to give N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid (1.87 g, 80%); ^{1}H NMR ($CDCl_3$) δ 9.61 (s, 1H), 8.75 (d, J=8.4 Hz, 1H), 7.63 (t, J=7.6 Hz, 1H), 7.47 (d, J=7.2 Hz, 1H), 7.06 (m, 2H), 6.83-6.80 (m, 1H), 5.58-5.51 (dd, J=4.2 and 11.7 Hz, 1H), 4.11 (q, J=7.0 Hz, 2H), 3.84 (s, 3H), 3.80-3.73 (m, 1H), 2.92-2.80 (m, 1H), 2.25 (s, 3H), 2.12-2.01 (m, 1H), 1.45 (t, J=7.0 Hz, 3H), 1.29 (d, J=6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.39, 169.21, 167.96, 149.01, 148.17, 137.36, 135.86, 131.61, 131.19, 124.75, 120.35, 117.95, 115.30, 112.90, 111.13, 64.88, 64.39, 55.88, 51.32, 39.92, 24.93, 23.77, 14.74.

EXAMPLE 27

N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.8 g, 4.2 mmol), pyridinium chlorochromate (1.44 g, 6.62 mmol) and Celite (0.7 g) in methylene chloride (40 mL) was stirred at room temperature for 4 hours. The mixture was filtered through celite and the filtrate was washed with water, brine, dried and concentrated. The crude product was purified by chromatography (silica gel, methylene chloride:ethyl acetate 9:1) to yield N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid; mp 81-83° C; ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 8.71 (d, J=8.4 Hz, 1H), 7.62 (t, 7.6 Hz, 1H), 7.45 (d, J=7.2 Hz, 1H), 7.06-7.03 (m, 2H), 6.83 (d, J=8.8 Hz, 1H), 5.73-5.67 (dd, J=5.2 and 9.9 Hz, 1H), 4.12 (q, J=7.0 Hz, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.46 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.17, 170.02, 169.14, 167.84, 149.14, 148.35, 137.34, 135.79, 131.29, 131.20, 124.65, 119.97, 117.88, 115.25, 112.48, 111.29, 64.39, 55.89, 49.92, 44.78, 30.13, 24.92, 14.70; Anal. Calcd. For $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.10; H, 5.68; N, 6.45.

EXAMPLE 28

N-{2-[1S-(3-Ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of S-4-amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol (1.5 g, 5.44 mmol), 3-acetamidophthalic anhydride (1.11 g, 5.44 mmol) and triethylamine (0.55 g, 5.44 mmol) in dimethylformamide (20 mL) was heated at 80-90° C for 7 hours. The mixture was concentrated in vacuo to an oil. The oil was dissolved in ethyl acetate and washed with water, brine, dried and concentrated. The crude product was purified by chromatography (silica gel, methylene chloride:ethyl acetate 8:2) to give N-{2-[1S-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-

yl}acetamide as a white solid (1.81 g, 78%); ^{1}H NMR ($CDCl_3$) δ 9.54-9.52 (d, 1H), 8.76-8.70 (m, 1H), 7.66-7.58 (m, 1H), 7.49-7.43 (m, 1H), 7.12-7.05 (m, 2H), 6.85-6.80 (m, 1H), 5.58-5.43 (m, 1H), 4.16-4.04 (q, 2H), 3.84 (s, 3H), 3.80-3.74 (m, 1H), 2.95-2.82 (m, 1H), 2.57-2.44 (m, 1H), 2.26 (s, 3H), 1.47 (t, 3H), 1.25 (d, 3H).

EXAMPLE 29

N-{2-[1S-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of N-{2-[1S-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.79 g, 4.2 mmol), pyridinium chlorochromate (1.43 g, 6.63 mmol) and celite (0.7 g) in methylene chloride (50 mL) was stirred at room temperature for 4 hours. The mixture was filtered through Celite and the filtrate was washed with water, brine, dried and concentrated. The crude product was purified by chromatography (silica gel, methylene chloride/ethyl acetate 9:1) to give N-{2-[1S-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide as a white solid (1.43 g, 79%); mp 80-82° C; ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 8.71 (d, J=8.4 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.46 (d, J=7.3 Hz, 1H), 7.06-7.03 (m, 2H), 6.83 (d, J=8.8 Hz, 1H), 5.73-5.67 (dd, J=5.2 and 9.9 Hz, 1H), 4.11 (q, J=7.0 Hz, 2H), 4.04-3.93 (dd, J=10.0 and 18.1 Hz, 1H), 3.83 (s, 3H), 3.28-3.19 (dd, J=5.3 and 18.1 Hz, 1H), 2.26 (s, 3H), 2.18 (s, 3H), 1.46 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.19, 170.04, 169.16, 167.86, 149.16, 148.36, 137.36, 135.80, 131.31, 131.22, 124.67, 119.99, 117.90, 115.27, 112.49, 111.30, 64.41, 55.90, 49.93, 44.80, 30.15, 24.94, 14.72; Anal. Calcd. For $C_{23}H_{24}N_2O_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 65.05; H, 5.77; N, 6.61.

EXAMPLE 30

4-Amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione

A mixture of 4-amino-4-(3-ethoxy-4-methoxyphenyl)butan-2-ol hydrochloride (1.0 g, 3.63 mmol), 3-amino-N-ethoxycarbonylphthalimide (0.85 g, 3.63 mmol) and triethylamine (2.37 g, 3.63 mmol) in dimethylformamide (15 mL) was heated at 80-90° C for 16 hours. The mixture was concentrated in vacuo and the residue was stirred with methylene chloride (10 mL). The mixture was filtered and the filtrate was concentrated and purified by chromatography (silica gel, methylene chloride:ethyl acetate 8:2) to give 4-amino-2-[1-(ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione as a white solid (0.72 g, 52%); ^{1}H NMR ($CDCl_3$) δ 7.41-7.35 (m, 1H), 7.11-7.05 (m, 3H), 6.83-6.80 (m, 2H), 5.54-5.48 (dd, J=4.1 and 11.8 Hz, 1H), 5.22 (s, 2H), 4.10 (q, 2H), 3.85 (s, 3H), 3.77 (m, 1H), 2.88-2.77 (m, 1H), 2.07-1.00 (m, 1H), 1.67 (s, 1H), 1.45 (t, 3H), 1.27 (d, 3H).

EXAMPLE 31

4-Amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione

A mixture of 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione (0.7 g, 1.82 mmol), pyridinium chlorochromate (0.79 g, 3.64 mmol) and Celite (0.6 g) in methylene chloride (40 mL) was stirred at room temperature for 4 hours. The mixture was filtered through celite and the filtrate was washed with water, brine, dried and concentrated. The residue was purified by chromatography (silica gel, methylene chloride:ethyl acetate 95:5) to give 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione as a white solid (0.49 g, 71%); ^{1}H NMR ($CDCl_3$) δ 7.38-7.31 (t, J=7.3 Hz, 1H), 7.08-7.05 (m, 3H), 6.81-6.77 (m, 2H), 5.74-5.67 (dd, J=5.9 and 9.4 Hz, 1H), 5.20 (s, 2H), 4.11 (q, J=7.0 Hz, 2H), 3.98-3.87 (dd, J=9.5 and 17.8 Hz, 1H), 3.83 (s, 3H), 3.33-3.23 (dd, J=5.6 and 17.7 Hz, 1H), 2.18-(s, 3H), 1.44 (t, J-6.9 Hz, 3H).

EXAMPLE 32

2-[1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione

A mixture of 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione (0.35 g, 0.92 mmol) and 2,5-dimethoxytetrahydrofuran (0.12 g, 0.92 mmol) in glacial acetic acid (5 mL) was refluxed for 1 hr. The mixture was dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate, water, brine, dried and concentrated. The residue was purified by chromatography (silica gel, methylene chloride:ethyl acetate 95:5) to 2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione as a yellow solid (0.27 g, 69%); mp 93-95° C; ^{1}H NMR ($CDCl_3$) δ 7.77-7.55 (m, 3H), 7.14-7.08 (m, 4H), 6.80 (d, J=8.8 Hz, 1H), 6.39-6.37 (m, 2H), 5.77-5.71 (dd, J=5.5 and 9.8 Hz, 1H), 4.10 (q, J=7.0 Hz, 1H), 4.05-3.93 (dd, J=9.8 and 18.0 Hz, 1H), 3.82 (s, 3H), 3.31-3.22 (dd, J=5.4 and 18.0 Hz, 1H), 2.16 (s, 3H), 1.44 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.27, 167.27, 166.13, 149.09, 148.25, 138.39, 135.11, 133.99, 131.39, 129.92, 122.06, 121.28, 120.74, 120.29, 112.69, 111.28, 110.66, 64.38, 55.89, 50.16, 44.69, 30.13, 14.69; Anal. Calcd. For $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.49; H, 5.65; N, 6.33.

EXAMPLE 33

2-Chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindol-4-yl}acetamide

A mixture of 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione (0.9 g, 2.34 mmol) amd chloroacetyl chloride (0.29 g, 2.57 mmol) in tetrahydrofuran (20 mL) was heated to reflux for 10 minutes. The mixture was concentrated in vacuo to give 2-chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.07 g, 100%); ^{1}H NMR ($CDCl_3$) δ 10.56 (s, 1H), 8.71 (d, J=8.4 Hz, 1H), 7.66 (t, J=7.6 Hz, 1H), 7.53 (d, J=7.3 Hz, 1H), 7.09-7.05 (m, 2H), 6.82 (d, J=8.0Hz, 1H), 5.75-5.69 (dd, J=5.3 and 9.8 Hz, 1H), 4.22 (s, 2H), 4.12 (q,

J=7.1 Hz, 2H), 4.04-3.93 (m, 1H), 3.83 (s, 3H), 3.31-3.21 (dd, J=5.2 and 18.0 Hz, 1H), 2.18 (s, 3H), 1.45 (t, J=7.0 Hz, 3H).

EXAMPLE 34

2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide Hydrochloride

A mixture of 2-chloro-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.07 g, 2.34 mmol) and N,N-dimethylamine (2.0 M in methanol, 3.5 mL, 7.0 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature for 16 hours. The solvent was removed in vacuo to give an oil. The oil was purified by chromatography (silica gel, methylene chloride:ethyl acetate 7:3) to give a white solid. To a solution of the solid in ethyl acetate (10 mL) was added hydrogen chloride in ether (1N, 4 mL). The slurry was filtered and washed with ether to give 2-(dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide hydrochloride as a white solid (0.52 g, 44%); mp 100-102° C; ^{1}H NMR (DMSO-d_6) δ 10.63 (s, 1H), 10.27 (s, 1H), 8.21 (d, J=8.2 Hz, 1H), 7.84 (t, J=7.7 Hz, 1H), 7.67 (d, J=7.3 Hz, 1H), 6.98 (s, 1H), 6.89 (s, 2H), 5.63-5.57 (dd, J=6.0 and 8.8 Hz, 1H), 4.19 (b, 2H), 3.99 (q, J=6.9 Hz, 2H), 3.77-3.67 (m, 1H), 3.74 (s, 3H), 3.52-3.42 (dd, J=6.1 and 18.1 Hz, 1H), 2.84 (s, 6H), 2.12 (s, 3H), 1.30 (t, J=6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 205.81, 167.32, 167.14, 164.84, 148.49, 147.76, 135.85, 134.29, 131.74, 131.48, 127.70, 119.48, 119.27, 119.09, 112.19, 111.76, 63.76, 58.32, 55.48, 48.90, 44.27, 43.47, 29.87, 14.69; Anal. Calcd. For $C_{25}H_{30}N_3O_6Cl$: C, 59.58; H, 6.00; N, 8.34; Cl, 7.03. Found: C, 59.18; H, 6.03; N, 8.14; Cl, 6.68.

EXAMPLE 35

4-Amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione

A mixture of 4R-amino-4R-(3-ethoxy-4-methoxyphenyl)butan-2-ol hydrochloride (4.0 g, 14.5 mmol), 3-amino-N-ethoxycarbonylphthalimide (3.57

g, 15.2 mmol) and triethylamine (1.47 g, 14.5 mmol) in dimethylformamide (60 mL) was heated at 80-90° C for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate, washed with water, brine, dried and concentrated. The crude product was purified by chromatography (silica gel, methylene chloride/ethyl acetate 8/2) to give 4-amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione (2.3 g, 41%) as a yellow solid;

EXAMPLE 36

4-Amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione

A mixture of 4-amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]isoindoline-1,3-dione (2.2 g, 5.72 mmol), pyridinium chlorochromate (2.5 g, 11.44 mmol) and celite (2 g) in methylene chloride (110 mL) was stirred at room temperature for 4 hours. The mixture was filtered through celite and the filtrate was washed with water, brine, dried, and concentrated. The residue was purified by chromatography (silica gel, methylene chloride:ethyl acetate 95:5) to give 4-amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione (1.23 g, 56%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.38-7.32 (m, 1H), 7.08-7.05 (m, 3H), 6.81-6.78 (m, 2H), 5.74-5.68 (dd, J=5.8 and 9.3 Hz, 1H), 5.20 (b, 2H), 4.11 (q, J=6.9 Hz, 2H), 3.98-3.87 (dd, J=9.5 and 17.8 Hz, 1H), 3.82 (s, 3H), 3.33-3.23 (dd, J=5.6 and 17.8 Hz, 1H), 2.17-(s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.37, 169.98, 168.58, 148.89, 148.22, 145.19, 135.04, 132.48, 131.96, 120.94, 119.98, 112.62, 112.54, 112.20, 111.06, 64.31, 60.36, 55.88, 49.54, 45.08, 30.18, 14.70.

EXAMPLE 37

2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione

A mixture of 4-amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione (0.34 g, 0.89 mmol) and 2,5-

dimethoxytetrahydrofuran (0.12 g, 0.93 mmol) in glacial acetic acid (5 mL) was refluxed for 1 hr. The mixture was dissolved in ethyl acetate (50 mL) and washed with saturated sodium bicarbonate, water, brine, dried and concentrated. The residue was purified by chromatography (silica gel, methylene chloride:ethyl acetate 95:5) to give 2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione (0.23 g, 60%) as a yellow solid; mp 90-92° C; ^{1}H NMR ($CDCl_3$) δ 7.73-7.56 (m, 3H), 7.15-7.08 (m, 4H), 6.81 (d, J=8.8 Hz, 1H), 6.39-6.38 (m, 2H), 5.77-5.71 (dd, J=5.4 and 9.8 Hz, 1H), 4.10 (q, J=6.9 Hz, 2H), 4.05-3.94 (dd, J=9.8 and 18.1 Hz, 1H), 3.82 (s, 3H), 3.31-3.22 (dd, J=5.4 and 18.1 Hz, 1H), 2.16 (s, 3H), 1.45 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.28, 167.27, 166.13, 149.08, 148.24, 138.39, 135.11, 133.99, 131.38, 129.03, 122.05, 121.28, 120.75, 120.28, 112.66, 111.26, 110.66, 64.37, 55.89, 50.15, 44.69, 30.14, 14.69; Anal. Calcd. For $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.49; H, 5.65; N, 6.33.

EXAMPLE 38

2-(Dimethylamino)-N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide Hydrochloride

A mixture of 4-amino-2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]isoindoline-1,3-dione (0.9 g, 2.34 mmol) and chloroacetyl chloride (0.29 g, 2.58 mmol) in tetrahydrofuran (20 mL) was heated to reflux for 10 minutes to give crude 2-chloro-N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide, which was stirred with N,N-dimethylamine (2.0 M in methanol, 3.5 mL) in tetrahydrofuran (15 mL) at room temperature for 16 hours. The mixture was concentrated in vacuo to an oil. The oil was purified by chromatography (silica gel, methylene chloride:ethyl acetate 75:25) to give a white solid. To the solid in ethyl acetate (10 mL) was added 1N hydrochloric acid in ether (4 mL). The slurry was filtered and washed with ether to give 2-(dimethylamino)-N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide

hydrochloride as a white solid (0.45 g, %); mp 118-120° C; ^{1}H NMR (DMSO-d_6) δ 10.60 (s, 1H), 10.29 (s, 1H), 8.16 (d, J=8.2 Hz, 1H), 7.84 (t, J=7.6 Hz, 1H), 7.67 (d, J=7.2 Hz, 1H), 6.97 (s, 1H), 6.88 (s, 2H), 5.62-5.56 (dd, J=5.9 and 8.8 Hz, 1H), 4.27 (s, 2H), 3.98 (q, J=7.0 Hz, 2H), 3.77-3.66 (m, 1H), 3.70 (s, 3H), 3.51-3.41 (dd, J=6.0 and 18.1 Hz, 1H), 2.88 (s, 6H), 2.11 (s, 3H), 1.30 (t, J=6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 205.81, 167.18, 167.12, 164.35, 148.49, 147.76, 135.83, 134.11, 131.78, 131.47, 128.05, 119.64, 119.42, 119.26, 112.17, 111.76, 63.76, 57.88, 55.48, 48.90, 44.25, 43.27, 29.88, 14.70; Anal. Calcd. For $C_{25}H_{30}N_3O_6Cl + 0.27\ H_2O$: C, 59.01; H, 6.05; N, 8.26; Cl, 6.97. Found: C, 59.06; H, 6.09; N, 8.14; Cl, 6.97.

EXAMPLE 39

Tablets, each containing 50 mg of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diaminoisoindoline-1,3-dione, can be prepared in the following manner:

<u>Constituents</u> (for 1000 tablets)	
2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4,5-diamino-isoindoline-1,3-dione	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the

addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 40

Tablets, each containing 100 mg of 7-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-e]benzimidazole-6,8-dione, can be prepared in the following manner:

Constituents (for 1000 tablets)

7-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-e]benzimidazole-6,8-dione	100.0 g
lactose	100.0 g
wheat starch	47.0 g
magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 41

Tablets for chewing, each containing 75 mg of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-3-pyrrolino[3,4-f]quinoxaline-1,3-dione, can be prepared in the following manner:

Composition (for 1000 tablets)

2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-

3-pyrrolino[3,4-f]quinoxaline-1,3-dione	75.0 g
mannitol	230.0 g
lactose	150.0 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 42

Tablets, each containing 10 mg N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide, can be prepared in the following manner:

Composition (for 1000 tablets)	
N-{2-[1-(3-ethoxy-4-methoxy-phenyl)-3-oxobutyl]-1,3-dioxo-isoindolin-4-yl}acetamide	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 43

Gelatin dry-filled capsules, each containing 100 mg of N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide, can be prepared in the following manner:

Composition (for 1000 capsules)

N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}-acetamide	100.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is sieved into the N-{2-[1R-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 44

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

2-(dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}-acetamide hydrochloride	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralized water	to 2500.0 mL

2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide hydrochloride is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms,

portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

EXAMPLE 45

Cyclopentyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}carboxamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-aminoisoindoline-1,3-dione (0.85 g, 2.0 mmol) and cyclopentanecarbonyl chloride (0.8 mL, 6.6 mmol) was heated at 100° C for 30 min. The mixture was cooled to room temperature. Methanol (10 mL) was added to the mixture. The mixture was stirred at 0° C for 1h. The resulting suspension was filtered to yield a solid. This solid was stirred in ether (10 mL) for 1h. The suspension was filtered and washed with ether to give cyclopentyl-N-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}carboxamide as a white solid (400 mg, 38% yield): mp, 134-136° C; ^{1}H NMR ($CDCl_3$) δ 1.49 (t, J = 6.9 Hz, 3H, CH_3), 1.57-2.06 (m, 8H, $C5H_8$), 2.76-2.83 (m, 1H, CH), 2.87 (s, 3H, CH_3), 3.75 (dd, J = 4.6, 14.4 Hz, 1H, CHH), 3.87 (s, 3H, CH_3), 4.12 (q, J = 7.0 Hz, 2H, CH_2), 4.56 (dd, J = 10.3, 14.4 Hz, 1H, CHH), 5.88 (dd, J = 4.5, 10.3 Hz, 1H, NCH), 6.84-6.87 (m, 1H, Ar), 7.10-7.14 (m, 2H, Ar), 7.48 (d, J = 7.2 Hz, 1H, Ar), 7.66 (t, J = 7.5 Hz, 1H, Ar), 8.79 (d, J = 8.4 Hz, 1H, Ar), 9.54 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ14.61, 25.81, 30.19, 30.23, 41.57, 47.14, 48.6, 554.62, 55.88, 64.47, 111.42, 112.41, 115.08, 117.92, 120.29, 124.98, 129.28, 130.98, 136.02, 137.89, 148.58, 149.71, 167.53, 169.48, 175.45; Anal Calcd for $C_{26}H_{30}N_2O_7S$ + 0.1 H_2O: C, 60.47; H, 5.89; N, 5.42; H_2O, 0.35. Found: C, 60.22; H, 5.67; N, 5.44; H_2O, 0.24.

EXAMPLE 46

3-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-aminoisoindoline-1,3-dione (0.80 g, 1.9 mmol) and 2-bromopropionyl

chloride (0.8 mL, 7.9 mmol) was heated at 100° C for 30 min. The mixture was cooled to room temperature. Methanol (10 mL) was added to the mixture. The solvent was removed in vacuo to give an oil. The oil was stirred in ether (10 mL) for 1 day. The resulting suspension was filtered and the solid washed with ether to give 3-bromo-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide as a yellow solid (0.84 g, 80% yield). A portion of the isolated bromide (620 mg, 1.2 mmol) and dimethylamine (2 mL, 2M in methanol, 4 mmol) was stirred at room temperature for 3 h. The resulting suspension was filtered and washed with methanol to yield the crude product as a yellow solid. The solid was purified by column chromatography to give 3-(dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide as a white solid (180 mg, 30% yield): mp, 163-165° C; ^{1}H NMR ($CDCl_3$) δ 1.47 (t, J = 6.9 Hz, 3H, CH_3), 2.38 (s, 6H, CH_3), 2.59 (t, J = 5.7 Hz, 2H, CH_2), 2.70 (t, J = 5.9 Hz, 2H, CH_2), 2.82 (s, 3H, CH_3), 3.78-3.85 (m, 1H, CH*H*), 3.86 (s, 3H, CH_3), 4.10 (q, J = 7.0 Hz, 2H, CH_2), 4.49 (dd, J = 9.8, 14.6 Hz, 1H, CH*H*), 5.86 (dd, J = 4.9, 9.7 Hz, 1H, NC*H*), 6.82-6.85 (m, 1H, Ar), 7.10-7.13 (m, 2H, Ar), 7.48 (d, J = 7.2 Hz, 1H, Ar), 7.63 (t, J = 7.5 Hz, 1H, Ar), 8.82 (d, J = 8.4 Hz, 1H, Ar), 11.36 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.62, 34.85, 41.49, 44.65, 48.74, 54.31, 55.01, 55.88, 64.44, 111.43, 112.52, 115.99, 117.93, 120.39, 120.08, 129.52, 131.42, 135.59, 137.33, 148.55, 149.67, 168.00, 168.16, 171.86; Anal Calcd for $C_{25}H_{31}N_3O_7S$: C, 58.01; H, 6.04; N, 8.12. Found: C, 57.75; H, 5.86; N, 7.91.

EXAMPLE 47

2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide, hydrogen chloride

Step 1: A solution of 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione (500 mg, 1.20 mmol) and 2-bromopropionyl bromide (0.140 mL, 1.34 mmol) in methylene chloride (10

mL) was stirred at room temperature overnight. An additional 0.1 mL of 2-bromopropionyl bromide (1 mol) was added and the mixture stirred overnight. To the mixture was added brine (4 mL), Sodium bicarbonate (sat, 10 mL) and methylene chloride (15 mL). The organic layer was separated, was washed with brine (10 mL), and dried over magnesium sulfate. The solvent was removed in vacuo to give a yellow oil. The oil was slurried in ether (10 mL). The resulting suspension was filtered and the solid washed with ether to give 2-bromo-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide as a white solid (500 mg, 76% yield): ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J = 6.9 Hz, 3H, CH_3), 1.97 (d, J = 6.9 Hz, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.75 (dd, J = 4.5, 14.4 Hz, 1H, CH*H*), 3.85 (s, 3H, CH_3), 4.49-4.59 (m, 2H, CH*H*, C*H*), 4.09(q, J = 6.9 Hz, 2H, CH_2), 5.87 (dd, J = 4.4, 10.3 Hz, 1H, NC*H*), 6.82-6.85 (m, 1H, Ar), 7.09-7.13 (m, 2H, Ar), 7.53 (d, J = 7.3 Hz, 1H, Ar), 7.68 (t, J = 7.5 Hz, 1H, Ar), 8.73 (d, J = 8.4 Hz, 1H, Ar), 10.19 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 14.61, 22.42, 41.54, 43.78, 48.67, 54.44, 55.87, 64.45, 111.39, 112.3, 116.10, 116.79, 120.35, 124.76, 129.14, 131.13, 136.02, 136.82, 148.55, 149.70, 167.28, 168.42, 169.11.

Step 2: To asuspension of 2-bromo-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide (500 mg, 0.9 mmol) in acetonitrile (5 mL) was added dimethylamine in methanol (1.5 mL, 2M, 3.0 mmol) at room temperature and the mixture was stirred for 2 days. The mixture was diluted with methylene chloride (50 mL) and sodium hydrogen carbonate (25 mL). The organic layer was separated, washed with brine (25 mL), and dried over magnesium sulfate. The solvent was removed in vacuo to give an oil. To a solution of the oil in ethyl acetate (20 mL) was added hydrogen chloride in ether (1.5 mL, 1N hydrogen chloride, 1.5 mmol). The resulting suspension was filtered and washed with ethyl acetate (10 mL) to give 2-(dimethylamino)-N-

{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}propanamide, hydrogen chloride as a white solid (290 mg, 58% yield): mp, 138-140° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 1.56 (brs, 3H, CH_3), 2.83 (brs, 6H, CH_3), 3.01 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.02 (q, J = 6.9 Hz, 2H, CH_2), 4.15 (dd, J = 4.4, 14.2 Hz, 1H, CH*H*), 4.27 (s, 1H, CH), 4.34 (dd, J = 10.6, 14.3 Hz, 1H, CH*H*), 5.78 (dd, J = 4.3, 10.3 Hz, 1H, NC*H*), 6.91-6.99 (m, 2H, Ar), 7.72 (d, J = 7.1 Hz, 1H< Ar), 7.87 (d, J = 7.5 Hz, 1H, Ar), 8.14 (m, 1H, Ar), 10.4 (brs, 1H, *H*Cl), 10.71 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 13.42, 14.67, 41.07, 41.47, 47.31, 52.98, 55.51, 52.74, 63.84, 111.75, 112.31, 119.70, 120.16, 128.92, 129.47, 131.80, 134.05, 135.87, 147.87, 148.91, 166.66, 166.86, 167.65, 168.53; Anal Calcd for $C_{25}H_{31}N_3O_7S$ + 1.1 HCl +0.6 H_2O: C, 52.82; H, 5.90; N, 7.39, Cl, 6.86, H_2O, 1.90. Found: C, 52.57; H, 5.77; N, 7.10; Cl, 6.90; H_2O, 1.47.

EXAMPLE 48

N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide hydrogen chloride

A mixture of N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-chloroacetamide (0.70 g, 1.41 mmol), and dimethylamine in tetrahydrofuran (2.4 mL, 2N, 4.8 mmol) in acetonitrile (15 mL) was stirred at room temperature overnight. The solvent was removed in vacuo to yield an oil. The oil was stirred in ethanol (5 mL). The suspension was filtered and washed with ethanol to give a white solid. To a solution of the solid in ethyl acetate (5 mL) was added hydrogen chloride in ether (1.5 mL, 1N). The resulting suspension was filtered and the solid was washed with ether to give N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide hydrogen chloride as a yellow solid (480 mg, 63% yield); mp, 192-194° C; ^{1}H NMR (DMSO-d6) δ 1.33 (t, J = 6.9 Hz, 3H, CH_3), 2.87 (s, 6H, 2CH_3), 3.03 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 4.02 (q, J = 7.0 Hz, 2H, CH_2), 4.16

(dd, J = 4.2, 14.3 Hz, 1H, CH*H*), 4.25 (brs, 2H, CH_2), 4.34 (dd, J = 10.8, 14.4 Hz, 1H, CH*H*), 5.79 (dd, J = 4.2, 10.4 Hz, 1H, NC*H*), 6.92-6.99 (m, 2H, Ar), 7.08 (s, 1H, Ar), 7.69 (d, J = 7.3 Hz, 1H, Ar), 7.88 (t, J = 7.7 Hz, 1H, Ar), 8.21-8.27 (m, 1H, Ar), 10.29 (s, 1H, *H*Cl), 10.64 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.65, 41.04, 43.36, 47.23, 52.86, 55.51, 58.09, 63.86, 111.79, 112.39, 119.22, 119.68, 127.78, 127.99, 129.42, 131.76, 134.25, 134.34, 135.95, 147.87, 148.92, 164.60, 166.79; Anal Calcd for $C_{24}H_{29}N_3O_7S$ + 1 HCl: C, 53.38; H, 5.60; N, 7.78; Cl, 6.56. Found: C, 53.52; H, 5.70; N, 7.61; Cl, 6.44.

EXAMPLE 49

N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide hydrogen chloride

A mixture of N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-chloroacetamide (1.79 g, 3.61 mmol), and dimethylamine in tetrahydrofuran (6.1 mL, 2N, 12.2 mmol) in acetonitrile (17 mL) was stirred at room temperature overnight. The solvent was removed in vacuo to give an oil. The oil was stirred in ethanol (10 mL). The resulting suspension was filtered and the solid washed with ethanol to give a white solid. The solid was purified by column chromatography (Silica Gel, 1:3 ethyl acetate:methylene chloride) to give a white solid (900 mg, 50% yield). To this solid in ethyl acetate (10 mL) was added hydrogen chloride in ether (2.6 mL, 1N). After 5 min, ether (10 mL) was added to this solution to give a suspension. The suspension was filtered and the solid washed with ether to give N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide hydrogen chloride as a yellow solid (830 mg, 86% yield); mp, 202-204° C; ^{1}H NMR (DMSO-d6) δ 1.33 (t, J = 6.9 Hz, 3H, CH_3), 2.87 (s, 6H, 2CH_3), 3.03 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 4.02 (q, J = 7.0 Hz, 2H, CH_2), 4.16 (dd, J = 4.2, 14.3 Hz, 1H, CH*H*), 4.25 (brs, 2H, CH_2), 4.34 (dd, J = 10.8, 14.4 Hz, 1H, CH*H*), 5.79 (dd, J = 4.2, 10.4 Hz, 1H, NC*H*), 6.92-6.99 (m, 2H,

Ar), 7.08 (s, 1H, Ar), 7.69 (d, J = 7.3 Hz, 1H, Ar), 7.88 (t, J = 7.7 Hz, 1H, Ar), 8.21-8.27 (m, 1H, Ar), 10.29 (s, 1H, *H*Cl), 10.64 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.65, 41.04, 43.36, 47.23, 52.86, 55.51, 58.09, 63.86, 111.79, 112.39, 119.22, 119.68, 127.78, 127.99, 129.42, 131.76, 134.25, 134.34, 135.95, 147.87, 148.92, 164.60, 166.79; Anal Calcd for $C_{24}H_{29}N_3O_7S$ + 1 HCl + 0.6 H_2O: C, 52.33; H, 5.71; N, 7.63; Cl, 6.44; H_2O, 1.96. Found: C, 52.46; H, 5.63; N, 7.46; Cl, 6.43; H_2O, 2.16.

EXAMPLE 50

4-{3-[(Dimethylamino)methyl]pyrrolyl}-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione, hydrogen chloride

A mixture of 1-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}pyrrole-3-carbaldehyde (0.840 g, 1.69 mmol), dimethylamine in tetrahydrofuran (2.6 mL, 2N, 5.2 mmol), and molecular sieves in methylene chloride (10 mL) was stirred at room temperature overnight. The mixture was cooled to 0° C. To the mixture was added methanol (10 mL), and sodium borohydride (32 mg, 0.84 mmol). After 1.5 h, the suspension was filtered thru a pad of magnesium sulfate. The magnesium sulfate pad was washed with methylene chloride (50 mL). The filtrate was washed with ammonium chloride (aq) (sat, 50 mL) and sodium hydrogen carbonate (sat, 50 mL). The solvent was removed in vacuo to give an oil. The oil was diluted with ethyl acetate (50 mL) and hydrogen chloride (100 mL, 1N). The organic layer was separated and was extracted with 1 N hydrogen chloride (2 x 100 mL). The combined aqueous layers was washed with ethyl acetate (30 mL), and then extracted with methylene chloride (3 X 50 mL). The combined methylene chloride layers were concentrated to give a solid. The solid was slurried in isopropanol (15 mL). The suspension was filtered and the solid washed with ethanol and then dried to yield 4-{3-[(dimethylamino)methyl]pyrrolyl}-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione, hydrogen chloride as a white solid (370 mg, 39% yield); mp, 158-160° C;

^{1}H NMR (CDCl$_3$) δ 1.46 (t, J = 6.9 Hz, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.69 (dd, J = 4.2, 14 Hz, 1H, CHH), 3.84 (s, 3H, CH_3), 4.04-4.12 (m, 4H, CH_2, CH_2), 4.59 (dd, J = 11, 14 Hz, 1H, CHH),5.89 (dd, J = 4.2, 11 Hz, 1H, NCH), 6.50-6.52 (m, 1H, Ar), 6.83 (d, J = 8 Hz, 1H, Ar), 7.08-7.14 (m, 3H, Ar), 7.47 (brs, 1H, Ar), 7.63-7.67 (m, 1H, Ar), 7.75-7.83 (m, 2H, Ar), 12.46 (brs, 1H, ClH); ^{13}C NMR (CDCl$_3$) δ 14.63, 41.37, 41.42, 41.58, 48.67, 53.86, 54.16, 55.87, 64.48, 111.39, 112.20, 112.45, 112.58, 120.42, 121.59, 121.95, 123.10, 124.95, 128.97, 130.24, 133.68, 135.72, 137.37, 148.53, 149.72, 165.51, 166.69; Anal Calcd for $C_{27}H_{31}N_3O_6S$ + 1 HCl + 0.8 H_2O: C, 56.25; H, 5.87; N, 7.29; Cl, 6.15; H_2O, 2.50. Found: C, 56.51; H, 5.78; N, 7.08; Cl, 6.05; H_2O, 2.63.

EXAMPLE 51

Cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}carboxamide

A stirred mixture of 2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-aminoisoindoline-1,3-dione (1.3 g, 3.1 mmol) and cyclopropane carbonyl chloride (3 mL) was heated to reflux for 45 min. To the cooled mixture was added methanol (10 mL) at 0° C and the mixture stirred for 30 min. The solvent was removed in vacuo to give an oil. The oil was stirred in ethanol (10 mL) for 2 h to give a suspension. The suspension was filtered and the solid washed with ethanol to give cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}carboxamide as a white solid (1.3 g, 86% yield); mp, 140-141° C; ^{1}H NMR (CDCl$_3$) δ 0.92-0.99 (m, 2H, 2CHH), 1.11-1.17 (m, 2H, 2CHH), 1.48 (t, J = 6.9 Hz, 3H, CH_3), 1.61-1.71 (m, 1H, CH), 2.88 (s, 3H, CH_3), 3.75 (dd, J = 4.4, 14.3 Hz, 1H, CHH), 3.86 (s, 3H, CH_3), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 4.57 (dd, J = 10.4, 14.3 Hz, 1H, CHH), 5.89 (dd, J = 4.4, 10.3 Hz, 1H, NCH), 6.84-6.88 (m, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.48 (d, J = 7.2 Hz, 1H, Ar), 7.65 (t, J = 7.4 Hz, 1H, Ar), 8.76 (d, J = 8.5 Hz, 1H, Ar), 9.69 (s, 1H, NH); ^{13}C NMR (CDCl$_3$) δ 8.71, 14.62, 16.16, 41.58, 48.59,

54.60, 55.89, 64.50, 111.49, 112.44, 114.83, 117.91, 120.26, 124.99, 129.27, 130.99, 136.02, 137.77, 148.63, 149.76, 167.49, 169.52, 172.79; Anal Calcd for $C_{24}H_{26}N_2O_7S$: C, 59.25; H, 5.39; N, 5.76. Found: C, 58.92; H, 5.21; N, 5.56.

EXAMPLE 52

2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-4-pyrrolylisoindoline-1,3-dione

A stirred mixture of 2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-4-aminoisoindoline-1,3-dione (0.92 g, 2.3 mmol) and 2,5-dimethoxy tetrahydrofuran (0.30 mL, 2.3 mmol) in acetic acid (9 mL) was heated to reflux for 2h. The solvent was removed in vacuo to give an oil. The oil was purified by column chromatography (Silica Gel, 1:4 ethyl acetate:methylene chloride) to give 2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-4-pyrrolylisoindoline-1,3-dione as a yellow solid (0.64 g, 62 % yield): mp, 116-118° C; ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3H, CH_3), 3.71 (dd, J = 4, 14 Hz, 1H, CHH), 3.85 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.61 (dd, J = 11, 14 Hz, 1H, CHH), 5.92 (dd, J = 4, 11 Hz, 1H, NCH), 6.39 (t, J = 2.0 Hz, 2H, Ar), 6.82 (d, J = 8 Hz, 1H, Ar), 7.09-7.10 (m, 1H, Ar), 7.15-7.17 (m, 3H, Ar), 7.59-7.64 (m, 1H, Ar), 7.73-7.77 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 41.44, 48.73, 54.26, 55.83, 55.89, 110.75, 111.12, 120.55, 120.99, 121.07,128.99, 129.31, 130.11, 133.71, 135.37, 138.61, 149.16, 149.37, 165.77, 166.82; Anal Calcd for $C_{23}H_{22}N_2O_6S$: C, 60.78; H, 4.88; N, 6.16. Found: C, 60.58; H, 5.01; N, 5.88.

EXAMPLE 53

N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide Hydrogen chloride

A mixture of N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-chloroacetamide (1.3 g, 2.7 mmol), and dimethylamine in tetrahydrofuran (4.5 mL, 2N, 9.0 mmol) in acetonitrile (20 mL) was stirred at room temperature overnight. The solvent was removed in vacuo

to give an oil. The oil was stirred in ethanol (5 mL). The resulting suspension was filtered and the solid washed with ethanol to give a yellow solid. To a stirred solution of the solid in ethyl acetate (10 mL) was added hydrogen chloride in ether (3.0 mL, 1N). After 5 min, ether (10 mL) was added. The resulting suspension was filtered and washed with ether to yield N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}-2-(dimethylamino)acetamide hydrogen chloride as a yellow solid (1.07 g, 74% yield); mp, 178-180° C; ^{1}H NMR (DMSO-d6) δ 2.69 (brs, 6H, 2CH_3), 3.02 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.88 (brs, 2H, CH_2), 4.16 (dd, J = 4.2, 14.3 Hz, 1H, CH*H*), 4.34 (dd, J = 10.8, 14.4 Hz, 1H, CH*H*), 5.79 (dd, J = 4.2, 10.4 Hz, 1H, NC*H*), 6.92-6.97 (m, 2H, Ar), 7.10 (d, J = 1.4 Hz, 1H, Ar), 7.65 (d, J = 7.2 Hz, 1H, Ar), 7.85 (t, J = 7.7 Hz, 1H, Ar), 8.37-8.40 (m, 1H, Ar), 10.15 (s, 1H, *H*Cl), 10.68 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 41.06, 44.18, 47.31, 52.95, 55.55, 55.59, 59.85, 111.26, 111.65, 119.16, 119.69, 127.00, 129.49, 121.64, 134.99, 136.09, 148.71, 148.76, 166.92, 167.34; Anal Calcd for $C_{23}H_{27}N_3O_7S$ + 1.25 HCl + 0.4 H_2O: C, 50.94; H, 5.40; N, 7.75; Cl, 8.17; H_2O, 1.33. Found: C, 51.30; H, 5.50; N, 7.37; Cl, 8.28; H_2O, 1.68.

EXAMPLE 54

Cyclopropyl-N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}carboxamide

A stirred mixture of 2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-4-aminoisoindoline-1,3-dione (0.68 g, 1.7 mmol) and cyclopropane carbonyl chloride (1.3 mL) was heated to reflux for 25 min. To the mixture was added ethanol (10 mL) at 0° C and kept for 30 min. The solvent was removed in vacuo to give a oil. The oil was stirred in ether (20 mL) for 30 min to give a suspension. The suspension was filtered and the solid washed with ether to give a white solid. The solid was purified by column chromatography (Silica Gel, 10% ethyl acetate in methylene chloride) to give cyclopropyl-N-{2-[1-(3,4-dimethoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-

dioxoisoindolin-4-yl}carboxamide as a white solid (330 mg, 42% yield); mp, 130-132° C; ^{1}H NMR ($CDCl_3$) δ 0.92-0.98 (m, 2H, 2CH*H*), 1.09-1.14 (m, 2H, 2CH*H*), 1.61-1.64 (m, 1H, C*H*), 2.88 (s, 3H, C*H*$_3$), 3.73 (dd, *J* = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, C*H*$_3$), 3.90 (s, 3H, C*H*$_3$), 4.58 (dd, *J* = 10.4, 14.3 Hz, 1H, CH*H*), 5.90 (dd, *J* = 4.4, 10.3 Hz, 1H, NC*H*), 6.84 (d, *J* = 8 Hz, 1H, Ar), 7.09-7.14 (m, 2H, Ar), 7.47 (d, *J* = 7.2 Hz, 1H, Ar), 7.65 (t, *J* = 7.6 Hz, 1H, Ar), 8.75 (d, *J* = 8.4 Hz, 1H, Ar), 9.68 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 6.75, 16.13, 41.54, 48.43, 54.36, 55.81, 55.94, 110.98, 111.11, 114.78, 117.88, 120.27, 124.93, 129.30, 130.94, 136.00, 137.68, 149.19, 149.35, 167.45, 169.48, 172.79; Anal Calcd for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.10; H, 5.16; N, 5.78. .

EXAMPLE 55

Cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide

A stirred mixture of 7-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindolin-1-one (1.0 g, 2.5 mmol) and cyclopropane carbonyl chloride (1 mL) was heated to reflux for 7 min. To the cooled mixture was added methanol (3 mL) at 0° C and the mixture was stirred for 30 min. To the suspension was added ethanol (5 mL). The suspension was filtered and washed with ethanol to give cyclopropyl-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide as an off-white solid (1.0 g, 86% yield); mp, 115-117° C; ^{1}H NMR ($CDCl_3$) δ 0.86-0.93 (m, 2H, 2CH*H*), 1.07-1.14 (m, 2H, 2CH*H*), 1.46 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.63-1.73 (m, 1H, C*H*), 2.95 (s, 3H, C*H*$_3$), 3.68 (dd, *J* = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, C*H*$_3$), 4.07 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 4.20 (d, *J* = 16.7 Hz, 1H, CH*H*), 4.21 (dd, *J* = 9.9, 14.3 Hz, 1H, CH*H*), 4.44 (d, *J* = 16.7 Hz, 1H, CH*H*), 5.73 (dd, *J* = 4.3, 9.9 Hz, 1H, NC*H*), 6.84-7.02 (m, 4H, Ar), 7.44 (t, *J* = 7.8 Hz, 1H, Ar), 8.43 (d, *J* = 8.3 Hz, 1H, Ar), 10.46 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.24, 14.61, 16.10, 41.43, 47.81, 51.55, 55.75, 55.88, 64.56, 111.46, 112.09, 116.69, 116.99, 117.76, 119.17, 129.27, 133.54,

138.06, 141.22, 148.84, 149.67, 169.96, 172.59; Anal Calcd for $C_{24}H_{28}N_2O_6S$ + 0.9 H_2O: C, 58.98; H, 6.15; N, 5.73; H_2O, 3.32. Found: C, 58.62; H, 5.99; N, 5.53; H_2O, 3.15.

EXAMPLE 56

2-(Dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}acetamide hydrogen chloride

A mixture of 7-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindolin-1-one (1.0 g, 2 mmol), and dimethylamine in tetrahydrofuran (3.6 mL, 2N, 7.2 mmol) in acetonitrile (25 mL) was stirred at room temperature overnight. The solvent was removed in vacuo to give a solid. The solid was recrystallized from ethanol (10 mL) to give a white solid. To stirred solution of the solid in ethyl acetate (10 mL) was added hydrogen chloride in ether (2.5 mL, 1N). After 5 min, ether (10 mL) was added to give a suspension. The suspension was filtered and the solid washed with ether to give 2-(dimethylamino)-N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}acetamide hydrogen chloride as a yellow solid (780 mg, 74% yield); mp, 145-147° C; ^{1}H NMR (DMSO-d6) δ 1.32 (t, J = 7 Hz, 3H, CH_3), 2.87 (brs, 6H, 2CH_3), 3.03 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.92-4.05 (m, 3H, CH*H*, CH_2), 4.17 (d, J = 17.9 Hz, 1H, CH*H*), 4.31-4.41 (m, 3H, CH_2, CH*H*), 4.68 (d, J = 17.9 Hz, 1H, CH*H*), 5.88 (dd, J = 3.5, 10.7 Hz, 1H, NC*H*), 6.91-6.98 (m, 2H, Ar), 7.02 (s, 1H, Ar), 7.31 (d, J = 7.3 Hz, 1H, Ar), 7.59 (t, J = 7.9 Hz, 1H, Ar), 8.15 (d, J = 8.0 Hz, 1H, Ar), 10.17 (s, 1H, *H*Cl), 10.53 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.72, 40.99, 43.40, 46.20, 48.81, 53.69, 55.32, 58.11, 63.93, 111.98, 112.16, 118.19, 118.58, 119.16, 119.76, 130.01, 133.01, 135.29, 142.55, 148.07, 148.88, 163.88, 167.45; Anal Calcd for $C_{24}H_{31}N_3O_6S$ + 1.1 HCl + 1.5 H_2O: C, 51.78; H, 6.35; N, 7.55; Cl, 7.00; H_2O, 4.85. Found: C, 51.58; H, 6.13; N, 7.39; Cl, 6.87; H_2O, 3.34.

EXAMPLE 57

Cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide

A stirred mixture of 7-amino-2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindolin-1-one (1.7 g, 4.2 mmol) and cyclopropane carbonyl chloride (0.46 mL, 5.1 mmol) in tetrahydrofuran (10 mL) was heated to reflux for 15 min. To the mixture was added methanol (4 mL) at room temperature and the mixture stirred for 10 min. The solvent was removed in vacuo to give an oil. The oil was recrystallized from ethanol (20 mL) to give cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide as a white solid (1.4 g, 71% yield); mp, 172-174° C; ^{1}H NMR ($CDCl_3$) δ 0.86-0.93 (m, 2H, 2CH*H*), 1.07-1.14 (m, 2H, 2CH*H*), 1.46 (t, *J* = 6.9 Hz, 3H, CH_3), 1.63-1.73 (m, 1H, C*H*), 2.95 (s, 3H, CH_3), 3.68 (dd, *J* = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, CH_3), 4.07 (q, *J* = 7.1 Hz, 2H, CH_2), 4.20 (d, *J* = 16.7 Hz, 1H, CH*H*), 4.21 (dd, *J* = 9.9, 14.3 Hz, 1H, CH*H*), 4.44 (d, *J* = 16.7 Hz, 1H, CH*H*), 5.73 (dd, *J* = 4.3, 9.9 Hz, 1H, NC*H*), 6.84-7.02 (m, 4H, Ar), 7.44 (t, *J* = 7.8 Hz, 1H, Ar), 8.43 (d, *J* = 8.3 Hz, 1H, Ar), 10.46 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.24, 14.61, 16.10, 41.43, 47.81, 51.55, 55.75, 55.88, 64.56, 111.46, 112.09, 116.69, 116.99, 117.76, 119.17, 129.27, 133.54, 138.06, 141.22, 148.84, 149.67, 169.96, 172.59; Anal Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.87; H, 6.13; N, 6.12.

EXAMPLE 58

Cyclopropyl-N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide

A stirred mixture of 7-amino-2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindolin-1-one (0.91 g, 2.2 mmol) and cyclopropane carbonyl chloride (0.25 mL, 2.8 mmol) in tetrahydrofuran (10 mL) was heated to reflux for 15 min. The solvent was removed in vacuo to give a solid. The solid was recrystallized from ethanol (10 mL) to give cyclopro-

pyl-N-{2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindolin-4-yl}carboxamide as an off-white solid (0.61 g, 56% yield); mp, 173-175° C; ^{1}H NMR ($CDCl_3$) δ 0.86-0.93 (m, 2H, 2CH*H*), 1.07-1.14 (m, 2H, 2CH*H*), 1.46 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.63-1.73 (m, 1H, C*H*), 2.95 (s, 3H, C*H*$_3$), 3.68 (dd, *J* = 4.4, 14.3 Hz, 1H, CH*H*), 3.86 (s, 3H, C*H*$_3$), 4.07 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 4.20 (d, *J* = 16.7 Hz, 1H, CH*H*), 4.21 (dd, *J* = 9.9, 14.3 Hz, 1H, CH*H*), 4.44 (d, *J* = 16.7 Hz, 1H, CH*H*), 5.73 (dd, *J* = 4.3, 9.9 Hz, 1H, NC*H*), 6.84-7.02 (m, 4H, Ar), 7.44 (t, *J* = 7.8 Hz, 1H, Ar), 8.43 (d, *J* = 8.3 Hz, 1H, Ar), 10.46 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.24, 14.61, 16.10, 41.43, 47.81, 51.55, 55.75, 55.88, 64.56, 111.46, 112.09, 116.69, 116.99, 117.76, 119.17, 129.27, 133.54, 138.06, 141.22, 148.84, 149.67, 169.96, 172.59; Anal Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.73; H, 5.91; N, 5.69.

EXAMPLE 59

(3R)-3-[7-(Acetylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide

A stirred mixture of (3R)-3-(7-amino-1-oxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide (400 mg, 1 mmol) and acetyl chloride (0.1 mL, 1.4 mmol) in tetrahydrofuran (5 mL) was heated to reflux for 2h. To the mixture was added 50% sodium hydrogen carbonate (40 mL) and ethyl acetate (50 mL). The organic layer was washed with sodium hydrogen carbonate (sat, 20 mL), brine (20 mL), and dried over magnesium sulfate. The solvent was removed in vacuo to give an oil. The oil was purified by column chromatography (Silica Gel, 1.5:1 ethyl acetate:methylene chloride) to give (3R)-3-[7-(acetylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide as a white solid (0.25 g, 57% yield); mp, 88-90° C; ^{1}H NMR ($CDCl_3$) ~ 1.43 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 2.22 (s, 3H, C*H*$_3$), 2.90 (s, 3H, C*H*$_3$), 3.04 (dd, *J* = 5.5, 16 Hz, 1H, CH*H*), 3.09 (s, 3H, C*H*$_3$), 3.52 (dd, *J* = 9.5, 15 Hz, 1H, CH*H*), 3.84 (s, 3H, C*H*$_3$), 4.07 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 4.26 (d, *J* = 17 Hz, 1H, CH*H*), 4.44 (d, *J* = 17

Hz, 1H, CH*H*), 5.58 (dd, *J* = 5.5, 9.4 Hz, 1H, NC*H*), 6.81-6.84 (m, 1H, Ar), 6.92-7.01 (m, 3H, Ar), 7.41 (t, *J* = 7.8 Hz, 1H, Ar), 8.41 (d, *J* = 8.3 Hz, 1H, Ar), 10.37 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) ~ 14.65, 24.84, 35.47, 36.16, 37.31, 48.71, 53.54, 55.85, 64.44, 111.35, 112.44, 116.83, 117.40, 117.97, 119.10, 131.72, 132.84, 137.65, 141.53, 148.46, 149.06, 168.98, 169.41, 169.57; Anal Calcd for $C_{24}H_{29}N_3O_5$ + 0.7 H_2O: C, 63.76; H, 6.78; N, 9.29; H_2O, 2.79. Found: C, 63.89; H, 6.64; N, 9.14; H_2O, 2.70.

EXAMPLE 60

(3R)-3-[7-(Cyclopropylcarbonylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide

A mixture of (3R)-3-(7-amino-1-oxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide (450 mg, 1 mmol) and cyclopropane carbonyl chloride (0.13 mL, 1.4 mmol) in tetrahydrofuran (5 mL) was heated to reflux for 15 min. To the mixture was added 50% sodium hydrogen carbonate (40 mL) and ethyl acetate (50 mL). The organic layer was washed with sodium hydrogen carbonate (sat, 20 mL) and brine (20 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an oil. The oil was purified by column chromatography (Silica Gel, 1:1 ethyl acetate:methylene chloride) to give (3R)-3-[7-(cyclopropylcarbonylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide as a white solid (0.35 g, 67% yield); mp, 92-94° C; ^{1}H NMR ($CDCl_3$) ~ 0.82-0.89 (m, 2H, C*H*$_2$), 1.05-1.11 (m, 2H, C*H*$_2$), 1.43 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.64-1.70 (m, 1H, C*H*), 2.90 (s, 3H, C*H*$_3$), 3.05 (dd, *J* = 5.5, 16 Hz, 1H, CH*H*), 3.10 (s, 3H, C*H*$_3$), 3.52 (dd, *J* = 9.5, 15 Hz, 1H, CH*H*), 3.84 (s, 3H, C*H*$_3$), 4.07 (q, *J* = 7 Hz, 2H, C*H*$_2$), 4.26 (d, *J* = 17 Hz, 1H, CH*H*), 4.44 (d, *J* = 17 Hz, 1H, CH*H*), 5.60 (dd, *J* = 5.7, 9.4 Hz, 1H, NC*H*), 6.82 (d, *J* = 8.7 Hz, 1H, Ar), 6.93-6.99 (m, 2H, Ar), 7.39 (t, *J* = 7.9 Hz, 1H, Ar), 8.39 (d, *J* = 8.2 Hz, 1H, Ar), 10.59 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 8.04, 14.64, 16.03, 35.46, 36.19, 37.31, 48.72, 53.56, 55.85, 64.46, 111.41, 112.52, 116.56, 117.41, 117.82,

119.13, 131.79, 132.84, 137.84, 141.54, 148.48, 149.04, 169.50, 169.58, 172.51; Anal Calcd for $C_{26}H_{31}N_3O_5$ + 0.5 H_2O: C, 65.81; H, 6.80; N, 8.85; H_2O, 1.90. Found: C, 65.83; H, 6.72; N, 8.72; H_2O, 1.94.

EXAMPLE 61

3-{4-[2-(Dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide hydrogen chloride

Step 1: A solution of 3-[4-(2-chloroacetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.0 g, 2.2 mmol) and carbonyldiimidazole (367 mg, 2.26 mmol) in tetrahydrofuran (7 mL) was stirred at room temperature for 1h. To the mixture was added dimethylamine in tetrahydrofuran (1.3 mL, 2 N, 2.6 mmol) and the mixture was stirred for 2h. Water (60 mL) and methylene chloride (50 mL) were then added to mixture. The aqueous layer was separated and was extracted with ethyl acetate (50 mL). The combined organic layers was washed with brine/hydrogen chloride 1N (1:1, 50 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give 3-[4-(2-chloroacetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide as a yellow solid (1.1 g, 100 % yield), which was used in the next step without further purification.

Step 2: To a stirred solution of 3-[4-(2-chloroacetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide (1.1 g, 2.3 mmol) in acetonitrile (15 mL) was added dimethylamine in tetrahydrofuran (3.3 mL, 2 N, 6.6 mmol) at room temperature and kept for overnight. The solvent was removed *in vacuo* to give a solid. The solid was diluted with methylene chloride (50 mL) and sodium hydrogen carbonate (25 mL). The separated organic layer was dried over magnesium sulfate. The solvent was removed *in vacuo* to give a solid. The solid was purified with chromatography to give 3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-

dimethylpropanamide as a white solid (640 mg, 57% yield). To a stirred solution of 3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide in ethyl acetate (4 mL) was added hydrogen chloride in ether (2 mL, 1N, 2 mmol) at room temperature. The resulting suspension was filtered and washed ethyl acetate to give 3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide hydrogen chloride as a white solid (580 mg, 84 % yield): mp, 92-94o C; ^{1}H NMR (DMSO-d6) δ 1.30 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 2.75 (s, 3H, C*H*$_3$), 2.87 (s, 6H, 2C*H*$_3$), 2.98 (s, 3H, C*H*$_3$), 3.21 (dd, *J* = 5.7, 16.6 Hz, 1H, CH*H*), 3.61 (dd, *J* = 9.3, 16.5 Hz, 1H, CH*H*), 3.72 (s, 3H, C*H*$_3$), 3.98 (q, *J* = 6.9 Hz, 2H, C*H*$_2$), 4.26 (s, 2H, C*H*$_2$), 5.62 (dd, *J* = 5.6, 9.1 Hz, 1H, NC*H*), 6.90-6.91 (m, 2H, Ar), 7.01 (s, 1H, Ar), 7.65 (d, *J* = 7.2 Hz, 1H, Ar), 7.85 (t, *J* = 7.7 Hz, 1H, Ar), 8.21(d, *J* = 8.2 Hz, 1H, Ar), 10.25 (brs, 1H, *H*Cl), 10.56 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ14.72, 26.37, 34.41, 34.81, 36.59, 43.34, 50.43, 55.52, 58.02, 63.78, 11.79, 112.38, 119.52, 127.79, 131.88, 131.94, 134.19, 135.79, 147.76, 148.47, 164.52, 167.25, 167.40, 169.16; Anal Calcd for $C_{26}H_{32}N_4O_6$ + HCl + 0.48 H_2O: C, 57.65; H, 6.32; N, 10.34; Cl, 6.55; H_2O, 1.60. Found: C, 57.70; H, 6.28; N, 10.28, Cl, 6.81; H_2O, 1.61.

EXAMPLE 62

(3R)-3-[7-(2-Chloroacetylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide

A mixture of (3R)-3-[7-(2-chloroacetylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide (0.79 g, 1.7 mmol) and dimethylamine in tetrahydrofuran (2.5 mL, 2N, 5.0 mmol) in acetonitrile (15 mL) was stirred at room temperature overnight. The solvent was removed in vacuo to give an oil. The oil was dissolved in ethyl acetate (100 mL), washed with sodium hydrogen carbonate (2 X 20 mL, sat), brine (10 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a solid. The solid was slurried in ether/hexanes (10 mL each) over-

night to give a suspension. The suspension was filtered and the solid washed with hexanes to give (3R)-3-[7-(2-chloroacetylamino)-1-oxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide as a white solid (622 mg, 77% yield); mp, 116-118o C; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7 Hz, 3H, CH_3), 2.43 (brs, 6H, 2CH_3), 2.89 (s, 3H, CH_3), 3.04 (dd, J = 6.1, 15.3 Hz, 1H, CH*H*), 3.12 (s, 3H, CH_3), 3.13 (d, J = 16 Hz, 1H, CH*H*), 3.19 (d, J = 16 Hz, 1H, CH*H*), 3.44 (dd, J = 9.1, 15 Hz, 1H, CH*H*), 3.85 (s, 3H, CH_3), 4.07 (q, J = 7 Hz, 2H, CH_2), 4.17 (d, J = 17 Hz, 1H, CH*H*), 4.43 (d, J = 17 Hz, 1h, CH*H*), 5.67 (dd, J = 6.2, 9 Hz, 1H, NC*H*), 6.82 (d, J = 8.4 Hz, 1H, Ar), 6.91-7.02 (m, 3H, Ar), 7.43 (t, J = 7.9 Hz, 1H, Ar), 8.52 (d, J = 8.3 Hz, 1H, Ar), 11.38 (s, 1H, N*H*); ^{13}C NMR (CDCl3) δ 14.65, 35.41, 36.34, 37.41, 45.92, 48.27, 53.03, 55.85, 64.06, 64.38, 111.26, 112.66, 117.05, 117.76, 118.82, 119.10, 131.79, 132.59, 137.00, 141.76, 148.44, 148.94, 168.90, 169.66, 170.03 ; Anal Calcd for $C_{26}H_{34}N_4O_5$: C, 64.71; H, 7.10; N, 11.61. Found: C, 64.37; H, 6.96; N, 11.53.

EXAMPLE 63

(3R)-3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide hydrogen chloride

A mixture of (3R)-3-[4-(2-chloroacetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide (8.10 g, 16.6 mmol) and dimethylamine in tetrahydrofuran (27 mL, 2N, 54 mmol) in acetonitrile (150 mL) was stirred at room temperature overnight. The solvent was removed in vacuo to give an oil. The oil was dissolved in ethyl acetate (150 mL), washed with sodium hydrogen carbonate (2 X 50 mL, sat), brine (50 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a solid. The solid was purified by column chromatography (Silica Gel, 1.5% methanol in methylene chloride) to give (3R)-3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide as a white solid (6.3 g, 76%

yield). To the solid in ethyl acetate (40 mL) was added hydrogen chloride in ether (20 mL, 1N). The suspension was filtered and washed with ether to give (3R)-3-{4-[2-(dimethylamino)acetylamino]-1,3-dioxoisoindolin-2-yl}-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide hydrogen chloride as a yellow solid (6.4 g, 72% yield); mp, 122-124° C; ^{1}H NMR (DMSO-d6) δ 1.33 (t, J = 7 Hz, 3H, CH_3), 2.75 (s, 3H, CH_3), 2.89 (s, 6H, 2CH_3), 2.98 (s, 3H, CH_3), 3.22 (dd, J = 5.4, 16.5 Hz, 1H, CHH), 3.60 (dd, J = 9.2, 16.5 Hz, 1H, CHH), 3.71 (s, 3H, CH_3), 3.97 (q, J = 7 Hz, 2H, CH_2), 4.30 (s, 2H, CH_2), 5.62 (dd, J = 5.6, 8.7 Hz, 1H, NCH), 6.86-6.93 (m, 2H, Ar), 7.00 (s, 1H, Ar), 7.65 (t, J = 7.1 Hz, 1H, Ar), 7.84 (t, J = 7.5 Hz, 1H, Ar), 8.17 (d, J = 7.9 Hz, 1H, Ar), 10.49 (s, 1H, ClH), 10.64 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 14.72, 34.41, 34.81, 36.59, 43.21, 50.43, 55.53, 57.77, 63.78, 111.79, 112.38, 119.32, 119.45, 119.58, 127.97, 131.90, 131.95, 134.12, 135.77, 147.76, 148.47, 164.28, 167.24, 167.33, 169.15; Anal Calcd for $C_{26}H_{32}N_4O_6$ + HCl + 1.1 H_2O: C, 56.49; H, 6.42; N, 10.13; Cl, 6.41; H_2O, 3.58. Found: C, 56.33; H, 6.61; N, 9.95; H_2O, 3.51.

EXAMPLE 64

3-(1,3-Dioxo-4-pyrrolylisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-N,N-dimethylpropanamide

A mixture of 3-(1,3-dioxo-4-pyrrolylisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.29 g, 2.97 mmol), and carbonyldiimidazole (481 mg, 2.97 mmol) in tetrahydrofuran (13 mL) was stirred at room temperature for 2h. To the mixture was added dimethylamine in tetrahydrofuran (1.7 mL, 2N, 3.4 mmol) and the mixture stirred for an additional 2h. Water (70 mL) and methylene chloride (50 mL) was added to the mixture. The organic layer was separated, washed with brine (20 mL), and dried over magnesium sulfate. The solvent was removed in vacuo to give a brown solid. This solid was purified by column chromatography (silica gel, 1:5 ethyl acetate:methylene chloride + 0.1% MeOH) to give 3-(1,3-dioxo-4-pyrrolylisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-N,N-

dimethylpropanamide as a yellow solid (750 mg, 55% yield): mp, 105-107° C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.00 (s, 3H, 2CH_3), 3.04 (dd, J = 4.9, 16 Hz, 1H, CHH), 3.82 (s, 3H, CH_3), 3.91 (dd, J = 10.2, 16.6 Hz, 1H, CHH), 4.09 (q, J = 7 Hz, 2H, CH_2), 5.82 (dd, J = 4.9, 10.2 Hz, 1H, NCH), 6.35 (t, J = 2 Hz, 2H, Ar),6.77-6.81 (m, 1H, Ar), 7.11-7.15 (m, 4H, Ar), 7.52-7.56 (m, 1H, Ar), 7.63-7.71 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.65, 34.71, 35.34, 37.02, 51.52, 55.83, 64.32, 110.48, 111.22, 112.76, 120.24, 120.66, 121.35, 122.02, 129.75, 132.00, 134.06, 134.94, 138.23, 148.15, 148.93, 166.19, 167.34, 169.58; Anal Calcd for $C_{28}H_{27}N_3O_5$ + 0.15 H_2O: C, 67.30; H, 5.99; N, 8.85. Found: C, 67.16; H, 5.88; N, 8.92.

EXAMPLE 65

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-(imidazolyl-methyl)isoindoline-1,3-dione

A mixture of 4-(aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl)isoindoline-1,3-dione (1.38 g, 3.20 mmol), glyoxal (40%, 0.46 g, 3.20 mmol) and formaldehyde (37%, 0.26 g, 3.20 mmol) in dilute H_3PO_4 (20 mL, pH=2) was heated to 80-90° C. Ammonium chloride (0.17 g) was added to the mixture and the mixture was maintained at 80-90° C for 2 hours. The mixture was cooled to 15° C and basified to pH 8 with K_2CO_3. The mixture was extracted with methylene chloride and the methylene chloride solution was washed with water (30 mL), brine (30 mL) and dried. The solvent was removed and the residue was purified by chromatography (silica gel, methylene chloride: methanol 97:3) to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-(imidazolylmethyl)isoindoline-1,3-dione (0.5 g, 32%) as a white solid. To a solution of the solid in ethyl acetate (5 mL) was added hydrogen chloride in ether (2 mL, 1N). The resulting suspension was filtered and washed with ether to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-(imidazolylmethyl)isoindoline-1,3-dione hydrochloride(0.26 g) as a white

solid: mp 126-128° C; ^{1}H NMR (DMSO-d_6) δ 9.19 (s, 1H), 7.93-7.83 (m, 2H), 7.72 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 1.2 Hz, 1H), 7.01-6.92 (m, 2H), 5.89 (s, 2H), 5.83-5.77 (dd, J = 4.5, 10.1 Hz, 1H), 4.40-4.30 (dd, J = 10.4, 14.3 Hz, 1H), 4.21-4.14 (dd, J = 4.7, 14.4 Hz, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.73 (s, 3H), 3.00 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 167.57, 166.97, 148.94, 147.86, 136.21, 135.41, 134.21, 133.46, 131.76, 129.37, 127.88, 123.59, 122.20, 120.56, 119.86, 112.43, 111.72, 63.82, 55.51, 52.98, 47.53, 47.03, 41.12, 14.67; Anal. Calcd. for $C_{24}H_{26}N_3O_6SCl$ + 0.53 H_2O : C, 54.44; H, 5.15; N, 7.93; S, 6.06; Cl, 6.69. Found : C, 54.58; H, 5.11; N, 7.66; S, 6.23; Cl, 6.71.

EXAMPLE 66

N-({2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide

A stirred mixture of 4-(aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione (0.92 g, 2.13 mmol) and acetic anhydride (10 mL) was heated at reflux for 40 min and then cooled to room temperature. Excess acetic anhydride was removed in vacuo. The residue was dissolved in ethyl acetate (50 mL) and washed with 2N hydrogen chloride (20 mL), water (20 mL), brine (20 mL), and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, methylene chloride : ethyl acetate 75:25) to give N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide (0.56 g, 55%) as a white solid: mp 84-86° C; ^{1}H NMR ($CDCl_3$) δ 7.74-7.62 (m, 3H), 7.13-7.09 (m, 2H), 6.85-6.82 (m, 1H), 6.74-6.69 (m, 1H), 5.92-5.86 (dd, J = 4.5, 10.1 Hz, 1H), 4.73 (d, J = 6.3 Hz, 2H), 4.59-4.49 (dd, J = 10.5, 14.2 Hz, 1H), 4.12 (q, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.81-3.74 (m, 1H), 2.84 (s, 3H), 1.96 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.15, 168.58, 167.77, 149.64, 148.54, 138.05, 135.38, 134.39, 132.07, 129.32, 128.21, 122.73, 120.40, 112.41, 111.37, 64.45, 55.88, 54.61, 48.65, 41.55, 39.42, 23.08, 14.62;

Anal. Calcd. for $C_{23}H_{26}N_2O_7S$: C, 58.22; H, 5.52; N, 5.90; S, 6.76. Found : C, 57.87; H, 5.52; N, 5.65; S, 6.66.

EXAMPLE 67

2-Chloro-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide

Triethylamine (0.52 g, 5.11 mmol) was added to a stirred suspension of 4-(aminomethyl)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-isoindoline-1,3-dione hydrochloride(1.0 g, 2.13 mmol). The clear solution was cooled in an ice bath to 5° C. Chloroacetyl chloride (0.30 g, 2.56 mmol) was added keeping the temperature between 5-9° C. The mixture was stirred at 5° C for 30 min and then warmed to room temperature for 2 hours. The mixture was washed with water (2x30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, methylene chloride : ethyl acetate 7:3) to give 2-chloro-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide (1.0 g, 92%): ^{1}H NMR ($CDCl_3$) δ 7.84-7.65 (m, 4H), 7.14-7.12 (m, 2H), 6.86 (d, J = 8.9 Hz, 1H), 5.94-5.88 (dd, J = 4.6, 10.3 Hz, 1H), 4.79 (d, J = 6.5 Hz, 2H), 4.61-4.51 (dd, J = 10.4, 14.4 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.02 (s, 2H), 3.85 (s, 3H), 3.80-3.72 (dd, J = 4.6, 14.4 Hz, 1H), 2.86 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H).

EXAMPLE 68

2-(Dimethylamino)-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide hydrochloride

Dimethylamine/methanol (2.0 M, 2.95 mL) was added to a stirred solution of 2-chloro-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide (1.0 g, 1.96 mmol) in tetrahydrofuran and the mixture was stirred at room temperature for 24 hours. The tetrahydrofuran was removed in vacuo and the residue was dissolved in methylene chloride (60 mL). The methylene chloride

solution was washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, methylene chloride : methanol 97.5:2.5) to give 2-(dimethylamino)-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxoisoindolin-4-yl}methyl)acetamide (0.6 g, 59%). To as stirred solution of the amine in ethyl acetate (10 mL) was added 1N hydrogen chloride in ether (4 mL). The resulting suspension was filtered and washed with ether to give 2-(dimethylamino)-N-({2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]1,3-dioxoisoindolin-4-yl}methyl)acetamide hydrochloride(0.55 g) as a white solid : mp 103-105° C; ^{1}H NMR ($DMSO-d_6$) δ 10.06 (s, 1H), 9.37 (m, 1H), 7.83-7.73 (m, 3H), 7.10 (s, 1H), 6.97-6.92 (m, 2H), 5.82-5.76 (dd, J = 4.1, 10.2 Hz, 1H), 4.81 (d, J = 5.6 Hz, 2H), 4.38-4.32 (dd, J = 10.3, 14.1 Hz, 1H), 4.19-4.12 (dd, J = 4.4, 14.4 Hz, 1H), 4.05-3.08 (m, 4H), 3.73 (s, 3H0, 3.02 (s, 3H), 2.82 (s, 6H0, 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($DMSO-d_6$) δ 167.60, 167.20, 164.79, 148.88, 147.85, 137.84, 134.69, 133.36, 131.51, 129.59, 127.09, 122.14, 119.79, 112.41, 111.76, 63.84, 57.17, 55.49, 52.98, 47.29, 43.13, 41.09, 37.82, 14.67; Anal. Calcd. for $C_{25}H_{32}N_3O_7SCl$ + 0.56 H_2O : C, 53.23; H, 5.92; N, 7.45, S, 5.68; Cl, 6.28. Found : C, 53.22; H, 5.87; N, 7.37; S, 5.64; Cl, 6.52.

EXAMPLE 69

4-[Bis(methylsulfonyl)amino]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione

Methanesulfonyl chloride (0.3 g, 2.62 mmol) was added to a stirred suspension of 4-amino-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)-ethyl]isoindoline-1,3-dione (0.55 g, 1.31 mmol) and triethylamine (0.4 g, 3.93 mmol) in methylene chloride (60 mL) and the resulting mixture stirred for 24 hours. The mixture was then washed with sat. Sodium bicarbonate (25 mL), 1N hydrogen chloride (25 mL), H_2O (25 mL), brine (25 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The

residue was slurried in methanol : tetrahydrofuran (2:1) to give after isolation by filtration 4-[bis(methylsulfonyl)amino]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione (0.53 g, 70%) as a white solid : mp 277-279 ° C; ^{1}H NMR (DMSO-d_6) δ 8.05-7.95 (m, 3H), 7.11-6.92 (m, 3H), 5.78-5.74 (dd, J = 5.5, 9.1 Hz, 1H), 4.31-4.22 (m, 2H), 3.99 (q, J = 6.9 Hz, 2H), 3.73 (s, 3H), 3.55 (s, 6H), 2.95 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.11, 165.35, 148.96, 147.88, 138.63, 136.05, 132.60, 129.64, 129.31, 129.27, 125.26, 119.89, 112.33, 111.76, 63.73, 55.46, 53.38, 47.92, 43.50, 43.44, 41.15, 14.61; Anal. Calcd. for $C_{22}H_{26}N_2O_{10}S_3$: C, 45.95; H, 4.56; N, 4.87; S, 16.74. Found: C, 45.90; H, 4.40; N, 4.75; S, 16.55.

EXAMPLE 70

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-[(methylsulfonyl)amino]isoindoline-1,3-dione

A mixture of 4-[bis(methylsulfonyl)amino]-2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]isoindoline-1,3-dione (0.8 g, 1.39 mmol) and 2N NaOH (1.59 mL, 3.18 mmol) in CH_3CN (120 mL) was stirred at room temperature for 8 hours. The mixture was neutralized with 6N hydrogen chloride (0.6 mL) and then concentrated. The residue was dissolved in methylene chloride (90 mL), washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the resulting solid was slurried in ethanol (50 mL) to give after isolation by filtration 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-4-[(methylsulfonyl)amino]isoindoline-1,3-dione (0.6 g, 86%) as a white solid : mp 191-193 ° C; ^{1}H NMR (DMSO-d_6) δ 9.31 (s, 1H), 7.85-7.74 (m, 2H), 7.61 (d, J = 6.6 Hz, 1H), 7.08 (s, 1H), 7.00-6.91 (m, 2H), 5.80-5.74 (m, 1H), 4.38-4.28 (dd, J = 10.5, 14.3 Hz, 1H), 4.19-4.11 (dd, J = 4.5, 14.3 Hz, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.73 (s, 3H), 3.27 (s, 3H), 3.00 (s, 3H0, 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 167.43, 166.71, 148.92, 147.87, 136.26, 135.73, 131.91, 129.40, 125.01, 119.79, 118.39, 117.59, 112.41,

111.76, 63.83, 55.48, 53.00, 47.35, 41.06, 40.63, 14.64; Anal. Calcd. for $C_{21}H_{24}N_2O_8S_3$ + 0.05 didulfonamide: C, 50.56; H, 4.86; N, 5.60; S, 13.12. Found: C, 50.25; H, 4.81; N, 5.60; S, 13.12.

EXAMPLE 71

N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-3-hydroxypentyl]-1,3-dioxoisoindolin-4-yl} acetamide

A stirred mixture of 5-amino-5-(3-ethoxy-4-methoxyphenyl)pentan-3-ol hydrochloride(1.15 g, 3.97 mmol), 3-acetamidophthalic anhydride (0.82 g, 3.97 mmol) and triethylamine (0.4 g, 3.97 mmol) in DMF (20 mL) was heated at 80-90° C for 6 hours. The mixture was then concentrated in vacuo. The residue was dissolved in ethyl acetate (80 mL), washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride : ethyl acetate 8:2) to give N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxypentyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.35 g, 77%) ; ^{1}H NMR ($CDCl_3$) δ 9.52 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.3 Hz, 1H), 7.09-7.07 (m, 2H), 6.83-6.80 (m, 1H), 5.61-5.55 (J = 3.9, 11.9 Hz, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.84 (s, 3H), 3.47 (m, 1H), 2.97-2.86 (m, 1H), 2.25 (s, 3H), 2.06-1.95 (m, 1H), 1.78 (b, 1H), 1.62-1.52 (m, 2H), 1.45 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.39, 169.23, 168.11, 148.94, 148.14, 137.32, 135.83, 131.81, 131.19, 124.72, 120.30, 117.94, 115.31, 112.87, 111.09, 70.01, 64.36, 55.86, 51.29, 37.92, 30.46, 24.92, 14.73, 9.90.

EXAMPLE 72

N-{2-[1-(3-Ethoxy-4-methoxyphenyl)-3-oxopentyl]1,3-dioxoisoindolin-4-yl} acetamide

A mixture of N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-hydroxypentyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.35 g, 3.06 mmol), pyridinium chlorochromate (1.32 g, 6.12 mmol) and celite (0.6 g) in methylene chloride (35 mL)

was stirred for 5 hours. The mixture was filtered through celite and the filtrate was washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. Solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride : ethyl acetate 9:1) to give N-{2-[1-(3-ethoxy-4-methoxyphenyl)-3-oxopentyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.08 g, 81%) as a white solid : mp 137-139° C; ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.07-7.04 (m, 2H), 6.83 (d, J = 8.8 Hz, 1H), 5.76-5.70 (dd, J = 5.2, 10.1 Hz, 1H), 4.12 (q, J = 6.9 Hz, 2H), 4.02-3.90 (dd, J = 10.1, 17.9 Hz, 1H), 3.83 (s, 3H), 3.26-3.17 (dd, J = 5.2, 17.9 Hz, 1H), 2.49 (q, J = 7.3 Hz, 2H), 2.26 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 208.03, 170.02, 169.15, 167.86, 149.12, 148.33, 137.34, 135.76, 131.39, 131.22, 124.64, 120.00, 117.87, 115.29, 112.50, 111.27, 64.38, 55.89, 49.94, 43.51, 36.10, 24.92, 14.71, 7.52; Anal. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.74; H, 6.34; N, 6.38.

EXAMPLE 73

2-[(1R)-1-(3-Ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione

A stirred mixture of (4R)-amino-4-(3-ethoxy-4-methoxyohenyl)butan-2-ol hydrochloride(1.14 g, 4.14 mmol), 3-(pyrrolylmethyl)phthalic anhydride (0.94 g, 4.14 mmol) and triethylamine (0.42 g, 4.14 mmol) in DMF (25 mL) was heated at 80-90° C for 17 hours. The mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (80 mL), washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride:ethyl acetate 9:1) to give 2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione (1.27 g, 68%) : ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 7.3 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.12-7.08 (m, 2H), 6.95 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 8.0

Hz, 1H), 6.73-6.72 (m, 2H), 6.23-6.21 (m, 2H), 5.61-5.55 (dd, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.78 (m, 1H), 2.94-2.83 (m, 1H), 2.16-2.08 (m, 1H), 1.76 (s, 1H), 1.46 (t, J = 6.9 Hz, 3H), 1.29 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.86, 168.35, 148.94, 148.11, 138.35, 134.51, 132.43, 132.01, 131.77, 127.04, 122.37, 121.44, 120.55, 113.00, 111.09, 109.11, 64.98, 64.35, 55.87, 51.43, 48.52, 40.03, 23.68, 14.73.

EXAMPLE 74

2-[(1R)-1-(3-Ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione

A mixture of 2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-3-hydroxybutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione (1.26 g, 2.81 mmol), pyridinium chlorochromate (1.21 g, 5.62 mmol), and celite (0.6 g) in methylene chloride (35 mL) was stirred at room temperature for 4 hours. The mixture was filtered through celite and the filtrate was washed with water (30 mL), brine (30 mL). The organic layer of the filtrate was dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, Hexane:ethyl acetate 6:4) to give 2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-3-oxobutyl]-4-(pyrrolylmethyl)isoindoline-1,3-dione (0.83 g, 66%) as a white solid : mp 143-145° C; ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 7.3 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.10-7.06 (m, 2H), 6.93 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.73-6.71 (m, 2H), 6.22-6.21 (m, 2H), 5.78-5.72 (dd, J = 5.4, 9.8 Hz, 1H), 3.32-3.23 (dd, J = 5.4, 18.0 Hz, 1H), 2.18 (s, 3H), 1.46 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.31, 168.53, 167.83, 149.11, 148.33, 138.31, 134.43, 132.37, 132.04, 131.55, 127.05, 122.34, 121.46, 120.14, 112.59, 111.29, 109.08, 64.39, 55.91, 50.01, 48.53, 44.88, 30.17, 14.72; Anal. Calcd. for $C_{26}H_{26}N_2O_5$; C, 69.94; H, 5.87; N, 6.27. Found: C, 70.01; H, 6.01; N,6.08.

EXAMPLE 75

N-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A stirred mixture of 4-amino-4-(3-cyclopentyloxy-4-methoxyphenyl)butan-2-ol hydrochloride(1.20 g, 3.80 mmol), 3-acetamidophthalic anhydride (0.78 g, 3.80 mmol) and triethylamine (0.38 g, 3.80 mmol) in DMF (15 mL) was heated at 80-90° C for 7 hours. The mixture was allowed to cool to room temperature and poured into water (80 mL). The resulting mixture was extracted with EtOAC (3x30 mL). The combined ethyl acetate extracts were washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride : EtOAC 8:2) to give N-{2-1-(3-cyclopentyloxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.3 g, 73%) as a white solid : ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.08-7.03 (m, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.57-5.51 (dd, *J* = 4.2, 11.6 Hz, 1H), 4.78 (m, 1H), 3.81 (s, 3H), 3.77-3.74 (m, 1H), 2.91-2.81 (m, 1H), 2.25 (s, 3H), 2.13-1.60 (m, 10H), 1.29 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.38, 169.21, 168.06, 149.70, 147.50, 137.33, 135.84, 131.54, 131.20, 124.71, 120.28, 117.93, 115.31. 115.07, 111.55, 80.45, 64.89, 55.97, 51.35, 39.92, 32.73, 24.91, 24.04, 23.76, 21.02.

EXAMPLE 76

N-{2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide

A mixture of N-{2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-3-hydroxybutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.28g, 2.74 mmol), pyridinium chlorochromate (1.18 g, 5.48 mmol) and celite (0.6 g) in methylene chloride (35 mL) was stirred at room temperature for 5 hours. The mixture was filtered through celite and the filtrate was washed with water (30

mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride : ethyl acetate 9:1) to give N-{2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-1,3-dioxoisoindolin-4-yl}acetamide (1.09 g, 85%) as a white solide : mp 145-147° C; ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 8.70 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.07-7.01 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 5.73-5.67 (dd, J = 5.1, 9.8 Hz, 1H), 4.77 (m, 1H), 4.04-3.93 (dd, J = 10.0, 18.1 Hz, 1H), 3.80 (s, 3H), 3.28-3.19 (dd, J = 5.1, 18.0 Hz, 1H), 2.26 (s, 3H), 2.18 (s, 3H), 1.97-1.61 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 205.22, 170.03, 169.15, 167.82, 149.83, 147.70, 137.33, 135.77, 131.23, 124.63, 119.88, 117.87, 115.28, 114.57, 111.72, 80.46, 55.99, 49.94, 44.82, 32.75, 30.14, 24.92, 24.05; Anal. Calcd. for $C_{26}H_{28}N_2O_6$; C, 67.23; H, 6.08; N, 6.03. Found: C, 66.96; H, 6.06; N, 5.89.

EXAMPLE 77

2-[1-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione

A mixture of 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-4-aminoisoindoline-1, 3-dione (0.41 g, 0.97 mmol), 2,5-dimethoxytetrahydrofuran (0.14 g, 1.07 mmol) and acetic acid (2 mL) in 1,2-dichloroethane (10 mL) was refluxed for 1 hour. The mixture was diluted with methylene chloride (25 mL) and washed with water (2 x 20 mL), brine (20 mL) and dried. Solvent was removed and the residue was purified by chromatography (Silica gel, Hexane : ethyl acetate 6:4) to give 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxobutyl]-4-pyrrolylisoindoline-1,3-dione (0.41 g, 91%) as a white solid : mp 142-144° C; ^{1}H NMR ($CDCl_3$) δ 7.72-7.56 (m, 3H), 7.14-7.04 (m, 4H), 6.79 (d, J = 8.2 Hz, 1H), 6.38 (m, 2H), 5.77-5.71 (dd, J = 5.4, 9.8 Hz, 1H), 4.77 (m, 1H), 4.05-3.94 (dd, J = 9.9, 18.9 Hz, 1H), 3.79 (s, 3H), 3.30-3.21 (dd, J = 5.4, 18.0 Hz, 1H), 2.16 (s, 3H), 1.98-1.60 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 205.31, 167.21, 166.14,

149.75, 147.61, 138.35, 135.09, 133.98, 131.34, 129.91, 126.04, 121.31, 120.74, 120.20, 114.72, 111.68, 110.61, 80.38, 55.97, 50.18, 44.72, 32.74, 30.12, 24.03; Anal. Calcd. for $C_{28}H_{28}N_2O_5$; C, 71.17; H, 5.97; N, 5.93. Found: C, 71.09; H, 6.09; N, 5.80.

EXAMPLE 78

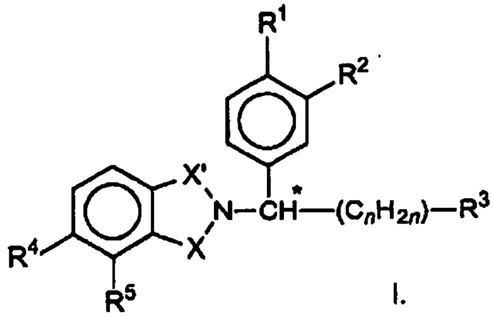
2-[1-(3,4-Dimethoxyphenyl)-3-oxobutyl]-4-[bis(methylsulfonyl)amino]isoindoline-1,3-dione

A mixture of 2-[1-(3,4-dimethoxyphenyl)-3-oxobutyl]-4-aminoisoindoline-1,3-dione (1.02 g, 2.77 mmol) and triethylamine (1.40 g, 13.85 mmol) in methylene chloride (40 mL) was cooled to 5 ° C. Methanesulfonyl chloride (1.27 g, 11.08 mmol) was added at 5-8 ° C and the resulting mixture was stirred at room temperature for 2 hours. The mixture was washed with sat. Sodium bicarbonate (20 mL), 1N hydrogen chloride (20 mL), water (30 mL), brine (30 mL) and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was purified by chromatography (Silica gel, methylene chloride : ethyl acetate 9:1) to give 2-[1-(3,4-dimethoxyphenyl)-3-oxobutyl]-4-[bis(methylsulfonyl)amino]isoindoline-1,3-dione (1.18 g, 81%) as a white solid : mp 194-196° C; ^1H NMR (DMSO-d_6) δ 8.02-7.93 (m, 3H), 6.99-6.90 (m, 3H), 5.65 (t, J = 6.7 Hz, 1H), 3.75-3.65 (m, 1H), 3.71 (s, 6H), 3.56 (s, 6H), 3.53-3.46 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 205.79, 166.58, 165.78, 148.64, 148.32, 138.48, 135.86, 132.68, 131.50, 129.85, 129.15, 125.06, 119.35, 111.58, 110.91, 55.49, 55.39, 49.27, 44.52, 43.53, 43.49, 29.92; Anal. Calcd. for $C_{22}H_{24}N_2O_8S_2$: C, 50.37; H, 4.61; N, 5.34, S, 12.23. Found: C, 50.43, H, 4.77; N, 5.16; S, 12.22.

What is claimed is:

1. A compound selected from the group consisting of (*a*) an isoindoline of the formula:

wherein:



I.

each of R^1 and R^2, independently of the other, is alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, cycloalkoxy of 3 to 18 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or cycloalkylmethoxy in which cycloalkyl has from 3 to 18 carbon atoms;

one of X and X' is =C=O or $=SO_2$ and the other of X and X' is a divalent group selected from =C=O, $=CH_2$, $=SO_2$ or $=CH_2C=O$;

R^3 is $-SO_2-Y$, -COZ, -CN, or hydroxyalkyl of 1 to 6 carbon atoms in which

Y is alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

Z is $-NR^{6*}R^{7*}$, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

R^{6*} is hydrogen, alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, or alkylamino of 1 to 4 carbon atoms;

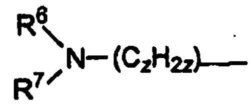
R^{7*} is hydrogen or alkyl of 1 to 4 carbon atoms;

n has a value of 1, 2, or 3;

(*i*) R^4 and R^5 when taken together, are $-NH-CH_2-R^8-$, $-NH-CO-R^8-$ or $-N=CH-R^8-$ in which $-R^8-$ is $-CH_2-$, -O-, -NH-, -CH=CH-, -CH=N-, or -N=CH-, or,

(*ii*) when are taken independently of each other,

(*1*) one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, pyrrolyl; oxadiazolyl, triazolyl, or



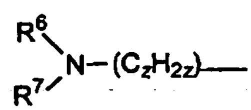
in which z is 0 or 1 provided z is not 0 when (*i*) R^3 is $-SO_2$-Y-COZ, or -CN and (*ii*) R^4 or R^5 is hydrogen;

R^6, when taken independently of R^7, is hydrogen; alkyl of 1 to 4 carbon atoms,cycloalkyl of 3 to 18 carbon atoms, alkanoyl of 2 to 5 carbon atoms, or cycloalkanoyl of 2 to 6 carbon atoms each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; alkoxyalkylcarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; or methylsulfonyl; and

R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, methylsufonyl; or or alkoxyalkylcarbonyl of 2 to 5 carbon atoms

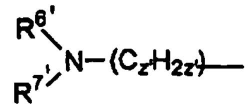
R^6 and R^7 taken together are -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms; or

(2) one of R^4 and R^5 is:



in which each of R^6, R^7, and z is as defined above; and

the other of R^4 and R^5 is



in which z' is 0 or 1;

$R^{6'}$ has the same meaning as, but is selected independently of, R^6;

$R^{7'}$ has the same meaning as, but is selected independently of, R^7; and

the carbon atom designated * constitutes a center of chirality; and

(*b*) the acid addition salts of said isoindoline derivatives which are susceptible of protonation.

2. A compound according to Claim 1 in which R^4 and R^5 together are -NH-CH_2-R^8-, -NH-CO-R^8- or -N=CH-R^8- in which -R^8- is -CH_2-, -O-, -NH-, -CH=CH-, -CH=N-, or -N=CH-.

3. A compound according to Claim 2 in which both X and X' are =C=O.

4. A compound according to Claim 2 in which one of X and X' is =C=O and the other of X and X' is $=CH_2$.

5. A compound according to Claim 2 in which one of X and X' is =C=O and the other of X and X' is $=SO_2$.

6. A compound according to Claim 2 in which each of R^1 and R^2, independently of the other, is methyl, ethyl, *n*-propyl, *i*-propyl, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclopentyl, cyclohexyl, cycloheptyl, or cyclopropylmethoxy.

7. A compound according to Claim 1 in which one of R^4 and R^5 is hydrogen and the other of R^4 and R^5 is imidazolyl, pyrrolyl, oxadiazolyl, or triazolyl:

8. A compound according to Claim 7 in which both X and X' are =C=O.

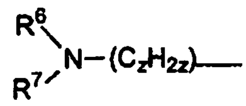
9. A compound according to Claim 7 in which one of X and X' is =C=O and the other of X and X' is $=CH_2$.

10. A compound according to Claim 7 in which one of X and X' is =C=O and the other of X and X' is $=SO_2$.

11. A compound according to Claim 7 in which each of R^1 and R^2, independently of the other, is methyl, ethyl, *n*-propyl, *i*-propyl, methoxy, ethoxy, *n*-propoxy, *i*-

propoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclopentyl, cyclohexyl, cycloheptyl, or cyclopropylmethoxy.

12. A compound according to Claim 1 in which one of R^4 and R^5 is:



in which *z* is 0 or 1 provided z is not 0 when (*i*) R^3 is $-SO_2-Y-COZ$, or -CN and (*ii*) R^4 or R^5 is hydrogen;

R^6, when taken independently of R^7, is hydrogen; alkyl of 1 to 4 carbon atoms,cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; or methylsulfonyl; and

R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, or methylsufonyl; or

R^6 and R^7 taken together are -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms.

13. A compound according to Claim 12 in which both X and X' are =C=O.

14. A compound according to Claim 12 in which one of X and X' is =C=O and the other of X and X' is $=CH_2$.

15. A compound according to Claim 12 in which one of X and X' is =C=O and the other of X and X' is $=SO_2$.

16. A compound according to Claim 12 in which each of R^1 and R^2, independently of the other, is methyl, ethyl, *n*-propyl, *i*-propyl, methoxy, ethoxy, *n*-propoxy, *i*-

propoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclopentyl, cyclohexyl, cycloheptyl, or cyclopropylmethoxy.

17. A compound according to Claim 12 in which R^6, when taken independently of R^7, is

hydrogen; alkyl of 1 to 4 carbon atoms,cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; or methylsulfonyl; and

R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, or methylsufonyl; or

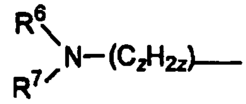
18 A compound according to Claim 17 in which R^6 is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, or methylsulfonyl.

19. A compound according to Claim 17 in which R^6 is alkanoyl of 2 to 5 carbon atoms, unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and

R^7 is hydrogen.

20. A compound according to Claim 12 in which R^6 and R^7 taken together are -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms.

21. A compound according to Claim 1 in which one of R^4 and R^5 is:



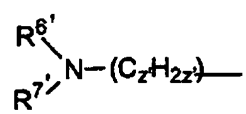
in which z is 0 or 1 provided z is not 0 when (*i*) R^3 is $-SO_2$-Y-COZ, or -CN and (*ii*) R^4 or R^5 is hydrogen;

R^6, when taken independently of R^7, is hydrogen; alkyl of 1 to 4 carbon atoms,cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; benzoyl; alkoxycarbonyl of 2 to 5 carbon atoms; N-morpholinocarbonyl; carbamoyl; N-substituted carbamoyl in which the substituent is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, or alkanoyl of 2 to 5 carbon atoms, each of which is unsubstituted or substituted with halo, amino, monoalkylamino or dialkylamino in which each alkyl group contains 1 to 4 carbon atoms; phenyl; benzyl; or methylsulfonyl; and

R^7 is hydrogen, alkyl of 1 to 4 carbon atoms, or methylsufonyl; or

R^6 and R^7 taken together are -CH=CH-CH=CH-, -CH=CH-N=CH-, or alkylidene of 1 or 2 carbon atoms substituted by amino, alkylamino, or dialkylamino in which each alkyl group has from 1 to 4 carbon atoms; and

the other of R^4 and R^5 is



in which *z'* is 0 or 1 provided z is not 0 when (*i*) R^3 is $-SO_2$-Y-COZ, or -CN and (*ii*) R^4 or R^5 is hydrogen;

$R^{6'}$ has the same meaning as, but is selected independently of, R^6; and

$R^{7'}$ has the same meaning as, but is selected independently of, R^7.

22. A compound according to Claim 21 in which both X and X' are =C=O.

23. A compound according to Claim 21 in which one of X and X' is =C=O and the other of X and X' is $=CH_2$.

24. A compound according to Claim 21 in which one of X and X' is =C=O and the other of X and X' is $=SO_2$.

25. A compound according to Claim 21 in which each of R^1 and R^2, independently of the other, is methyl, ethyl, *n*-propyl, *i*-propyl, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclopentyl, cyclohexyl, cycloheptyl, or cyclopropylmethoxy.

26 A compound according to Claim 21 in which each of R^6 and $R^{6'}$, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, or methylsulfonyl, and each of R^7 and $R^{7'}$ is hydrogen.

27. A compound according to Claim 21 in which each of R^6 and $R^{6'}$, independently of the other, is alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, alkylaminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and

each of R^7 and $R^{7'}$ is hydrogen.

28. A compound according to Claim 21 in which one of R^6 and $R^{6'}$ is alkanoyl of 2 to 5 carbon atoms, haloalkanoyl of 2 to 5 carbon atoms, aminoalkanoyl of 2 to 5 carbon atoms, benzoyl, alkoxycarbonyl of 2 to 5 carbon atoms, N-morpholinocarbonyl, carbamoyl, and N-substituted carbamoyl in which the substituent is methyl, ethyl, or trifluoromethyl; and

the other of R^6 and $R^{6'}$ is hydrogen, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms; phenyl, benzyl, or methylsulfonyl; and each of R^7 and $R^{7'}$ is hydrogen.

29. A compound according to Claim 1 which is a substantially chirally pure (S)-isomer or a substantially chirally pure (R)-isomer.

30. A compound according to Claim 1 which is a mixture of the (S)-isomer and the (R)-isomer.

31. The method of inhibiting PDE IV in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

32. A method of reducing or inhibiting undesirable levels of TNFα in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

33. A method of reducing or inhibiting undesirable levels of matrix metalloproteinases in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

34. A method of treating in a mammal a disease selected from the group consisting of inflammatory disease, autoimmune disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, aphthous ulcers, cachexia, graft versus host disease, asthma, adult respiratory distress syndrome, and acquired immune deficiency syndrome, which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

35. A method of treating cancer in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

36. A method of treating undesirable angiogenesis in a mammal which comprises administering thereto an effective amount of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers.

37. A pharmaceutical composition comprising (*i*) a quantity of a substantially chirally pure (R)- or (S)-isomer of a compound according to Claim 1 or a mixture of said isomers, that upon administration in a single or multiple dose regimen is pharmaceutically effective and (*ii*) a pharmaceutically acceptable carrier therefor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/30770

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 487/04, 471/04, 413/04, 403/04, 209/46, 209/48, 209/49; A61K 31/4188, 31/437, 31/4985, 31/4245, 31/4196, 31/4178, 31/4035; A61P 11/06

US CL : 544/345; 546/84, 548/131, 266.4, 302.1, 312.1, 466, 477; 514/250, 292, 364, 383, 387, 397, 414, 417

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/345; 546/84, 548/131, 266.4, 302.1, 312.1, 466, 477; 514/250, 292, 364, 383, 387, 397, 414, 417

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GIEMBYCZ, M.A. Phospodiesterase 4 Inhibitors and the Treatment of Asthma, Drugs February 2000, Vol. 59, No. 2, pages 193-212	34
Y	MULLER, G.W. et al, Thalidomide Analogs and PDE4 Inhibition, Bioorg. Med. Chem. Let., 1998, Vol. 8, pages 2669-2674.	1-31
A	DUPLANTIER, A.J. et al, 7-Oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridines as Novel Inhibitors of Human Eosinophil Phosphodiesterase, May, 1998, Vol. 41, No. 13, pages 2268-2277.	31-37
Y	MULLER, G.W. et al, Structural Modifications of Thalidomide Produce Analogs with Enhanced Tumor Necrosis Factor Inhibitory Activity, J. Med. Chem., 1996, Vol. 39, pages 3238-3240.	1-30 & 32
A	HE, W. et al, Novel Cyclic Compounds as potent Phosphodiesterase 4 Inhibitors, October 1998, Vol. 41, No. 22, pages 4216-4223.	31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Mukund Shah
Telephone No. (703) 308-1235

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(71) Applicant *(for all designated States except US)*: CELGENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MAN, Hon-Wah [US/US]; 102 Bermuda Drive, Neshanic Station, NJ 08853 (US). MULLER, George [US/US]; 250 Windmill Court, Bridgewater, NJ 08807 (US). HUANG, Shaei, Y. [—/US]; 81 Daly Court, Perth Amboy, NJ 08861 (US).

(74) Agents: COLLINS, Bruce, M. et al.; Mathews, Collins, Shepherd & Gould, P.A., Suite 306, 100 Thanet Circle, Princeton, NJ 08540 (US).

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(54) Title: SUBSTITUTED ACYLHYDROXAMIC ACIDS AND METHOD OF REDUCING TNFα LEVELS

(57) Abstract: Imido and amido substituted acylhydroxamic acids which reduce the levels of TNFα and inhibit phosphodiesterase in a mammal. A typical embodiment is (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)propanoate.

SUBSTITUTED ACYLHYDROXAMIC ACIDS AND METHOD OF REDUCING TNFα LEVELS

Field of the Invention

The present invention relates to imido and amido substituted acylhydroxamic acids, the method of reducing levels or activities of cytokines such as tumor necrosis factor α in a mammal through the administration thereof, and pharmaceutical compositions of such derivatives.

Background of the Invention

Tumor necrosis factor-α (TNFα) is a cytokine which is released primarily by cells of immune systems in response to certain immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, cachexia, and acute phase responses similar to those seen during acute infections, inflammatory diseases, and shock states. Excessive or unregulated TNFα production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome [Tracey, *et al.*, *Nature* 330, 662-664 (1987) and Hinshaw, *et al.*, *Circ. Shock* 30, 279-292 (1990)], rheumatoid arthritis, inflammatory bowel disease, cachexia [Dezube, *et al.*, *Lancet*, 335 (8690), 662 (1990)], and lupus. TNFα concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from Adult Respiratory Distress Syndrome (ARDS) patients [Millar, *et al.*, *Lancet* 2(8665), 712-714 (1989)]. Systemic infusion of recombinant TNFα resulted in changes typically seen in ARDS [Ferrai-Baliviera, *et al.*, *Arch. Surg.* 124(12), 1400-1405 (1989)].

TNFα appears to be involved in a number of bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption. TNFα apparently contributes to this mechanism. [Bertolini, *et al.*, *Nature* 319, 516-518 (1986) and Johnson, *et al.*, *Endocrinology* 124(3), 1424-1427 (1989)]. TNFα also has been shown to stimulate bone resorption and inhibit bone formation *in vitro* and *in vivo* through stimulation of osteoclast formation and activation combined with inhibition of osteoblast functions. Another compelling link with disease is the association between production of TNFα by tumor or host tissues and malignancy associated hypercalcemia [*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)]. In Graft versus Host Reactions, increased serum TNFα levels have been associated with major complication following acute allogenic bone marrow transplants [Holler, *et al.*, *Blood*, 75(4), 1011-1016 (1990)].

Validation of TNF-α inhibition as a clinical therapy has been demonstrated by the therapeutic use of TNF-α antibodies and soluble TNF-α receptors. TNFα blockage with monoclonal anti-TNFα antibodies has been shown to be beneficial in rheumatoid arthritis [Elliot, *et al.*, *Int. J. Pharmac.* 1995 17(2), 141-145]. High levels of TNFα are associated with Crohn's disease [von Dullemen, *et al.*, *Gastroenterology*, 1995 109(1), 129-135] treatment with soluble TNFα receptor treatment gave clinical benefits .

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Elevated levels of serum TNFα correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks [Grau, *et al.*, *N. Engl. J. Med.* 320(24), 1586-1591 (1989)].

TNFα plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibodies to TNFα completely blocked the silica-induced lung fibrosis in mice [Pignet, *et al.*, *Nature*, 344, 245-247 (1990)]. High levels of TNFα production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis [Bissonnette, *et al.*, *Inflammation* 13(3), 329-339 (1989)]. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNFα as compared with macrophages from normal donors [Baughman, *et al.*, *J. Lab. Clin. Med.* 115(1), 36-42 (1990)].

Elevated levels of TNFα are implicated in reperfusion injury, the inflammatory response which follows reperfusion, and is a major cause of tissue damage after blood flow loss [Vedder, *et al.*, *PNAS* 87, 2643-2646 (1990)]. TNFα also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity, suppressing the anticoagulant protein C pathway, and down-regulating the expression of thrombomodulin [Sherry, *et al.*, *J. Cell Biol.* 107, 1269-1277 (1988)]. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. TNFα-induced expression of adhesion molecules, such as intercellular adhesion molecules (ICAM) or endothelial leukocyte adhesion molecules (ELAM) on endothelial cells may be especially important [Munro, *et al.*, *Am. J. Path.* 135(1), 121-132 (1989)].

It has been reported that TNFα is a potent activator of retrovirus replication including activation of HIV-1. [Duh, *et al., Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll, *et al., Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto, *et al., Blood* 79, 2670 (1990); Clouse, *et al., J. Immunol.* 142, 431-438 (1989); Poll, *et al., AIDS Res. Hum. Retrovirus*, 191-197 (1992)]. At least three types or strains of HIV (*i.e.*, HIV-1, HIV-2 and HIV-3) have been identified. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T-lymphocyte requires T-lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T-lymphocytes after T-cell activation. This virus protein expression and/or replication is mediated or maintained by this T-cell activation. Once an activated T-lymphocyte is infected with HIV, the T-lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNFα, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T-lymphocyte activation. Therefore, interference with cytokine activity such as prevention or inhibition of cytokine production, notably TNFα, in an HIV-infected individual assists in limiting the maintenance of T-lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [Rosenberg, *et al., The Immunopathogenesis of HIV Infection*, Advances in Immunology, 57 (1989)]. Cytokines, such as TNFα, have been shown to activate HIV replication in monocytes and/or macrophages [Poli, *et al., Proc. Natl. Acad. Sci.*, 87, 782-784 (1990)], therefore, prevention or inhibition of

cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNFα as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells [Osborn, *et al.*, *PNAS* 86 2336-2340]. This evidence suggests that a reduction of TNFα synthesis may have an antiviral effect in HIV infections, by reducing transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNFα [Folks, *et al.*, *PNAS* 86, 2365-2368 (1989)]. A molecular mechanism for the virus inducing activity is suggested by TNFα's ability to activate a gene regulatory protein (NFκB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) [Osborn, *et al.*, *PNAS* 86, 2336-2340 (1989)]. TNFα in AIDS associated cachexia is suggested by elevated serum TNFα and high levels of spontaneous TNFα production in peripheral blood monocytes from patients [Wright, *et al.*, *J. Immunol.* 141(1), 99-104 (1988)]. TNFα has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

The nuclear factor κB (NFκB) is a pleiotropic transcriptional activator (Lenardo, *et al., Cell* 1989, 58, 227-29). NFκB has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNFα and active HIV transcription [Dbaibo, *et al., J. Biol. Chem.* 1993, 17762-66; Duh, *et al., Proc. Natl. Acad. Sci.* 1989, 86, 5974-78; Bachelerie, *et al., Nature* 1991, 350, 709-12; Boswas, *et al., J. Acquired Immune Deficiency Syndrome* 1993, 6, 778-786; Suzuki, *et al., Biochem. And Biophys. Res. Comm.* 1993, 193, 277-83; Suzuki, *et al., Biochem. And Biophys. Res Comm.* 1992,

189, 1709-15; Suzuki, *et al., Biochem. Mol. Bio. Int.* 1993, 31(4), 693-700; Shakhov, *et al., Proc. Natl. Acad. Sci. USA* 1990, 171, 35-47; and Staal, *et al., Proc. Natl. Acad. Sci. USA* 1990, 87, 9943-47]. Thus, it would be helpful to inhibit NFκB activation, nuclear translation or binding to regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful to inhibit a multitude of disease states.

Many cellular functions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). Such cellular functions can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNFα and NFκB. Increased levels of cAMP also lead to the relaxation of airway smooth muscle.

The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE) [Beavo and Reitsnyder, *Trends in Pharm.*, 11, 150-155, 1990]. There are ten known members of the family of PDEs. It is well documented that the inhibition of PDE type IV (PDE 4) enzyme is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle [Verghese, et al., *Journal of Pharmacology and Experimental Therapeutics*, 272(3), 1313-1320, 1995].

Decreasing TNFα levels and/or increasing cAMP levels thus constitutes a valuable therapeutic strategy for the treatment of many inflammatory, infectious, immunological, and malignant diseases. These include but are not restricted to: septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis,

psoriasis and other dermal diseases, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, tumor growth, undesirable angiogenesis, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Prior efforts directed to the suppression of the effects of TNFα have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies [Beutler, *et al.*, *Science* 234, 470-474 (1985); WO 92/11383].

Angiogenesis, the process of new blood vessel development and formation, plays an important role in numerous normal and pathological physiological events. Angiogenesis occurs in response to specific signals and involves a complex process characterized by infiltration of the basal lamina by vascular endothelial cells in response to angiogenic growth signal(s), migration of the endothelial cells toward the source of the signal(s), and subsequent proliferation and formation of the capillary tube. Blood flow through the newly formed capillary is initiated after the endothelial cells come into contact and connect with a preexisting capillary. Angiogenesis is required for tumor growth beyond a certain size.

Inhibitory influences predominate in the naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis [Rastinejad, *et al.*, 1989, *Cell* 56:345-355]. In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of

pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail.

Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis [Moses, *et al.*, 1991, *Biotech.* 9:630-634; Folkman, *et al.*, 1995, *N. Engl. J. Med.*, 333:1757-1763; Auerbach, *et al.*, 1985, *J. Microvasc. Res.* 29:401-411; Folkman, 1985, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203; Patz, 1982, *Am. J. Opthalmol.* 94:715-743; and Folkman, *et al.*, 1983, *Science* 221:719-725]. In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data suggests that the growth of solid tumors is dependent on angiogenesis [Folkman and Klagsbrun, 1987, *Science* 235:442-447].

The maintenance of the avascularity of the cornea, lens, and trabecular meshwork is crucial for vision as well as for ocular physiology. See, *e.g.*, reviews by Waltman, *et al.*, 1978, *Am. J. Ophthal.* 85:704-710 and Gartner, *et al.*, 1978, *Surv. Ophthal.* 22:291-312. Currently, the treatment of these diseases, especially once neovascularization has occurred, is inadequate and blindness often results.

An inhibitor of angiogenesis could have an important therapeutic role in limiting the contributions of this process to pathological progression of the underlying disease states as well as providing a valuable means of studying their etiology. For example, agents that inhibit tumor neovascularization could play an important role in inhibiting metastatic and solid tumor growth.

Several kinds of compounds have been used to prevent angiogenesis. Taylor, *et al.* used protamine to inhibit angiogenesis, [Taylor, *et al.*, *Nature* 297:307 (1982)]. The toxicity of protamine limits its practical use as a therapeutic. Folkman, *et al.* used heparin and steroids to control angiogenesis. [Folkman, *et al.*, *Science* 221:719 (1983) and U.S. Pat. Nos. 5,001,116 and 4,994,443]. Steroids, such as tetrahydrocortisol, which lack gluco and mineral corticoid activity, are angiogenic inhibitors. Interferon β is also a potent inhibitor of angiogenesis induced by allogeneic spleen cells [Sidky, *et al.*, Cancer Research 47:5155-5161 (1987)]. Human recombinant interferon-α was reported to be successfully used in the treatment of pulmonary hemangiomatosis, an angiogenesis-induced disease [White, *et al.*, *New England J. Med.* 320:1197-1200 (1989)].

Other agents which have been used to inhibit angiogenesis include ascorbic acid ethers and related compounds [Japanese Kokai Tokkyo Koho No. 58-131978]. Sulfated polysaccharide DS 4152 also shows angiogenic inhibition [Japanese Kokai Tokkyo Koho No. 63-119500]. A fungal product, fumagillin, is a potent angiostatic agent *in vitro*. The compound is toxic *in vivo*, but a synthetic derivative, AGM 12470, has been used *in vivo* to treat collagen II arthritis. Fumagillin and *o*-substituted fumagillin derivatives are disclosed in EPO Publication Nos. 0325199A2 and 0357061A1.

In U.S. Pat. No. 5,874,081, Parish teaches use of monoclonal antibodies to inhibit angiogenesis. In WO92/12717, Brem, *et al.* teach that some tetracyclines, particularly Minocycline, Chlortetracycline, Demeclocycline and Lymecycline are useful as inhibitors of angiogenesis. Brem, *et al.* teach that Minocycline inhibits angiogenesis to an extent comparable to that of the combination therapy of heparin and cortisone [*Cancer Research*, 51, 672-675, Jan. 15, 1991]. Teicher, *et al.* teach

that tumor growth is decreased and the number of metastases is reduced when the anti-angiogenic agent of metastases is reduced when the anti-angiogenic agent Minocycline is used in conjunction with cancer chemotherapy or radiation therapy [*Cancer Research*, 52, 6702-6704, Dec. 1, 1992].

Macrophage-induced angiogenesis is known to be stimulated by TNFα. Leibovich, *et al.* reported that TNFα induces *in vivo* capillary blood vessel formation in the rat cornea and the developing chick chorioallantoic membranes at very low doses and suggested TNFα is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth [*Nature*, 329, 630-632 (1987)].

All of the various cell types of the body can be transformed into benign or malignant tumor cells. The most frequent tumor site is lung, followed by colorectal, breast, prostate, bladder, pancreas, and then ovary. Other prevalent types of cancer include leukemia, central nervous system cancers, brain cancer, melanoma, lymphoma, erythroleukemia, uterine cancer, bone cancer, and head and neck cancer.

Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites (*e.g.*, in the breast, colon, and skin) surgery cannot be used in the treatment of tumors located in other areas (*e.g.*, the backbone) nor in the treatment of disseminated neoplastic conditions (*e.g.*, leukemia). Chemotherapy involves the disruption of cell replication or cell metabolism. Chemotherapy is used most often in the treatment of leukemia, as well as breast, lung, and testicular cancer.

Chemotherapeutic agents are often referred to as antineoplastic agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids. Thus, it would be preferable to find less toxic compounds for cancer treatment.

Matrix metalloproteinase (MMP) inhibition has been associated with several activities including inhibition of TNFα [Mohler, *et al.*, *Nature*, 370, 218-220 (1994)] and inhibition of angiogenesis. MMPs are a family of secreted and membrane-bound zinc endopeptidases that play a key role in both physiological and pathological tissue degradation [Yu, *et al.*, *Drugs & Aging, 1997,* (3):229-244; Wojtowicz-Praga, *et al.*, *Int. New Drugs*, 16:61-75 (1997)]. These enzymes are capable of degrading the components of the extracellular matrix, including fibrillar and non-fibrillar collagens, fibronectin, laminin, and membrane glycoproteins. Ordinarily, there is a delicate balance between cell division, matrix synthesis, matrix degradation (under the control of cytokines), growth factors, and cell matrix interactions. Under pathological conditions, however, this balance can be disrupted. Conditions and diseases associated with undesired MMP levels include, but are not limited to: tumor metastasis invasion and growth, angiogenesis, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, Crohn's disease, inflammatory bowel disease, and corneal epidermal or gastric ulceration.

Increased MMP activity has been detected in a wide range of cancers [Denis, *et al.*, *Invest. New Drugs*, 15: 175-185 (1987)]. As with TNFα, MMPs are believed to be involved in the invasive processes of angiogenesis and tumor metastasis.

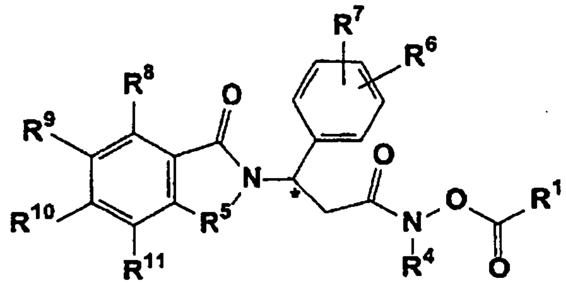
Detailed Description

The present invention is based on the discovery that certain classes of compounds more fully described herein decrease the levels of TNFα, increase cAMP levels, inhibit phosphodiesterases (PDEs, in particular PDE 4), affect tumors, and affect angiogenesis.

The compounds described herein can inhibit the action of NFκB in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, cancer, HIV, AIDS, and opportunistic infections in AIDS. TNFα and NFκB levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNFα and NFκB. Compounds in this application inhibit PDE4.

In particular, the invention pertains to

(a) compounds of the formula:



Formula I

wherein

the carbon atom designated * constitutes a center of chirality,

R^4 is hydrogen or –(C=O)–R^{12};

each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl methyl, pyridyl, imidazoyl, imidazolyl methyl, or $CHR^*(CH_2)_nNR^*R^0$

wherein $R^*$and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and n = 0, 1, 2;

R^5 is C=O, CH_2, CH_2-CO-, or SO_2;

each of R^6 and R^7, independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkoxy of 3 to 8 carbon atoms, halo, bicycloalkyl of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, 1-indanyloxy, 2-indanyloxy, C_4-C_8-cycloalkylidenemethyl, or C_3-C_{10}-alkylidenemethyl;

each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is

(i) hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, halo, or

(ii) one of R^8, R^9, R^{10}, and R^{11} is acylamino comprising a lower alkyl, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen, or

(iii) hydrogen if R^8 and R^9 taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(iv) hydrogen if R^{10} and R^{11}, taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(v) hydrogen if R^9 and R^{10} taken together are benzo; and

(b) The acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

The carbon atom designated with an * constitutes a center of chirality. Both optical isomers are part of this invention. Unless otherwise defined, the preferred R group of R-(C=O)- in acyl and the acyl of acylamino in this invention is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl, imidazolylmethlyl, or $CHR^*(CH_2)_nNR^*R^0$, wherein R^* and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and n = 0, 1, 2. Alkyl is preferably unbranched. Branched and/or cyclic alkyl forms are also envisioned.

Subgroups of Formula I can include the following: The acylhydroxamic acid derivative in Formula I, wherein R^4 is hydrogen; R^5 is C=O; R^8 is hydrogen; and one of R^9 and R^{11} is hydrogen and the other of R^9 and R^{11}, taken together with R^{10}, is benzo, methylenedioxy, dioxo, or dialkoxy. The acylhydroxamic acid derivative in Formula I, wherein R^4 is hydrogen; R^5 is C=O; R^8 and R^9 are hydrogen; and R^{10} and R^{11}, taken together, are methylenedioxy. The acylhydroxamic acid derivative in Formula I, wherein one or more of R^8, R^9, R^{10}, and R^{11}, independently of the others, is hydrogen, alkyl of 1 to 10 carbon atoms, or alkoxy of 1 to 10 carbon atoms. The acylhydroxamic acid derivative in Formula I, wherein R^8, R^9, R^{10}, and R^{11} are *(a)* at least one alkyl of 1 to 10 carbon atoms (*i.e.*, a lower alkyl) with the remainder of R^8, R^9, R^{10}, and R^{11} being hydrogen, or *(b)* at least one alkoxy of 1 to 10 carbon atoms with the remainder of R^8, R^9, R^{10}, and R^{11} being hydrogen. For the purposes of this invention, acylamino includes acetamido. The acylhydroxyamic acid derivative in Formula I, which is a substantially chirally pure (3R)-isomer, a substantially chirally pure (3S)-isomer, or a mixture thereof. The acylhydroxamic acid derivative in Formula I, wherein R^4 is hydrogen. The acylhydroxamic acid derivative in Formula I, wherein R^4 is –(C=0)-R^{12}. The acylhydroxamic acid derivative in Formula I, wherein each of R^8, R^9, R^{10}, and R^{11} is hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms. The acylhydroxamic acid derivative in Formula I, wherein one of R^8, R^9, R^{10}, or R^{11} is amino, acylamino, alkylamino, dialkylamino, or hydroxy. An acylhydroxamic acid derivative in Formula I, wherein R^1 is alkyl of 1 to 10 carbon atoms, pyridyl, or imidazolyl.

Unless otherwise defined, the term alkyl denotes a univalent saturated branched or straight hydrocarbon chain containing from 1 to 10 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and

tert-butyl. Alkoxy refers to an alkyl group bound to the remainder of the molecule through an ethereal oxygen atom. Representative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and tert-butoxy. Acetylamino also includes the name acetamido. Methylenedioxy may sometimes be called dioxo.

In Formula I, each of R^8, R^9, R^{10}, and R^{11} can be hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms. Alternatively, one of R^8, R^9, R^{10}, and R^{11} is amino, alkyl amino, dialkyl amino, or acyl amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or hydroxy, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen. Formula I, can also have R^8, R^9, R^{10}, and R^{11} as hydrogen. Formula I can be a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

A pharmaceutical composition can contain a quantity of an acylhydroxamic acid derivative of Formula I, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, sufficient upon administration in a single or multiple dose regimen to reduce or inhibit levels of TNFα or to treat cancer, undesired angiogenesis, or arthritis in a mammal in combination with a carrier. A pharmaceutical composition can contain a quantity of Formula I which is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, sufficient upon administration in a single or multiple dose regimen to inhibit undesirable levels of matrix metalloproteinases and/or PDE4 in a mammal in combination with a carrier.

This invention includes the following methods along with other reasonably expected methods. A method of reducing or inhibiting undesirable levels of TNFα in a mammal which comprises administering thereto an effective amount of an

acylhydroxamic acid derivative of Formula I, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof. A method of reducing or inhibiting undesirable levels of matrix metalloproteinases in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative of Formula I, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof. A method of treating in a mammal a disease selected from the group consisting of but not limited to inflammatory disease, autoimmune disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, aphthous ulcers, cachexia, graft versus host disease, asthma, adult respiratory distress syndrome, and acquired immune deficiency syndrome, which comprises administering thereto an effective amount of a compound described by Formula I, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof. A method of treating cancer in a mammal which comprises administering thereto an effective amount of a compound described by Formula I, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof. A method of treating undesirable angiogenesis in a mammal which comprises administering thereto an effective amount of a compound described by Formula I, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof. Also included in this invention is a method of reducing or inhibiting phosphodiesterases IV (PDE4) in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative described by Formula I, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (R)-isomer, or a mixture thereof.

The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα and/or inhibit phosphodiesterases, and/or inhibit inflammation and/or angiogenesis and/or cancer. Inhibition of the phosphodiesterase type 4 (PDE4 or PDE IV) is the preferred embodiment in this application. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment.

The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by inflammation excessive TNFα production, excessive MMPs, or where increased cAMP levels will be helpful, Some examples include viral infections, such as those caused by the herpes viruses or viral conjunctivitis, or dermal conditions such as psoriasis or atopic dermatitis, *etc.*

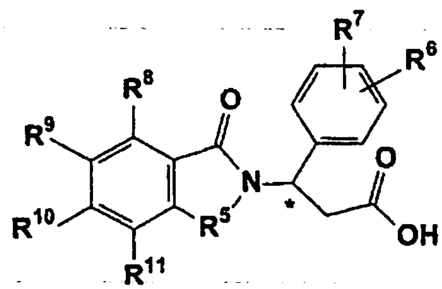
The compounds can also be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNFα production. TNFα mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

Angiogenesis, the process of new blood vessel development and formation, plays an important role in numerous physiological events, both normal and pathological. The compounds also can be used to inhibit unwanted angiogenesis. The compounds may also be used to inhibit tumor growth.

The invention also relates to MMP-inhibiting compounds, compositions thereof, and their use in the treatment of diseases and disorders associated with undesired production or activity of MMPs. These compounds are capable of inhibiting connective tissue breakdown, and are useful in the treatment or prevention of conditions involving tissue breakdown. These include, but are not limited to, tumor metastasis, invasion, and growth, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, and corneal epidermal inflammatory bowel disease, or gastric ulceration.

The following Formulas are related as follows. The compounds according to Formula III are the starting material for the compounds of Formula II. The compound of Formula II is the starting material for the compounds of Formula IV in Reaction a to produce the compound of Formula I(b).

The compounds of Formula IV are readily prepared by reacting a carboxylic acid of the formula:

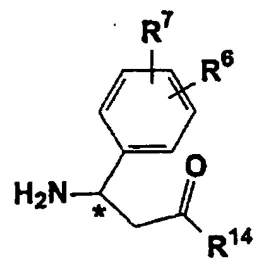


Formula II

with hydroxylamine hydrochloride or an alkoxyamine hydrochloride in the presence of a coupling agent. R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are defined above. The reaction generally is conducted in an inert solvent such as tetrahydrofuran, ethyl acetate, *etc.* under an inert atmosphere such as nitrogen. Ambient or above ambient

temperatures can be employed. When the reaction is substantially complete, generally the products can be readily isolated simply through the addition of water.

The compounds of Formula II which are here utilized as intermediates are described in U.S. Patent No. 5,605,914, the disclosure of which is incorporated herein by reference. Briefly, such intermediates can be prepared through the reaction of an amino acid of the formula:



Formula III

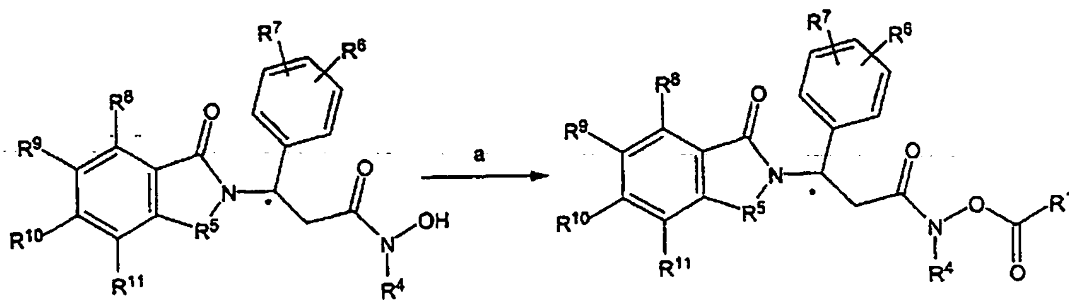
in which R^{14} is hydroxy, alkoxy, or a protecting group, with an anhydride, an N-carbethoxyimide, a dialdehyde, or an *o*-bromo aromatic acid.

Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also exhibit biological activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York,

1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol.15/I, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

In any of the foregoing reactions, a nitro compound can be employed with the nitro group being converted to an amino group by catalytic hydrogenation or chemical reaction. Alternatively, a protected amino group can be deprotected to yield the corresponding amino compound. An amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially benzyloxycarbonyl, formyl, or a lower alkanoyl group, each of which is branched in a 1- or α position to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, a lower alkanoyl group which is substituted in the position α to the carbonyl group, as for example trifluoroacetyl.

In a preferred embodiment, hydroxamic acids such as those prepared above can be reacted with acid anhydrides, in acetonitrile (CH_3CN) or other inert solvent as follows:

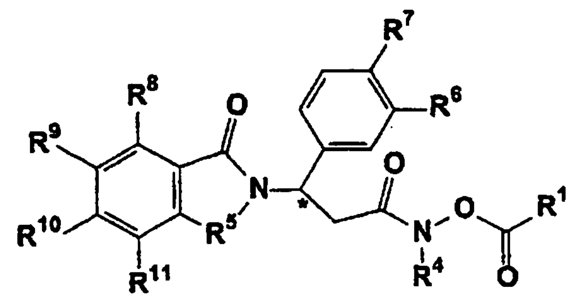


Formula IV Formula I(b)

in which Reaction a is a reaction of IV with an anhydride of the formula $(R^1CO)_2O$ in CH_3CN. R^1, R^4, R^5, and R^6 to R^{11} are defined above. A mixture of two main reaction products (A) and (B) may result. The first reaction product (A) has R^4 being hydrogen. The second reaction product (B) has R^4 being –(C=O)-R^{12}. R^{12} is defined above. Reaction products (A) and (B) can be purified by column chromatography. The crude product can also be slurried in hexane several times to afford pure reaction product (A). Reaction product (B), where R^{12} is not the same as R^1, can be prepared from treatment of (A) with an acid anhydride containing the desired R^{12} group. Formula I(b) is Formula I or can be a subgroup of Formula I.

The compounds of Formula I possess at least one center of chirality (designated by "*") and thus can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid or base, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α-bromocamphoric acid, methoxyacetic acid, tartaric acid, di-acetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; *i.e.*, in a form having an optical purity of >95%. Chiral bases can also be used for this process.

Formula I(c) is a subgroup of Formula I. Formula 1(c) represents *(a)* an acylhydroxamic acid derivative having the formula:



Formula 1(c)

in which

the carbon atom designated * constitutes a center of chirality,

R^4 is hydrogen or –(C=O)–R^{12};

each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl methyl, pyridyl, imidazoyl, imidazolyl methyl, or $CHR^*(CH_2)_nNR^*R^0$

wherein $R^*$and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and n = 0, 1, 2;

R^5 is C=O, CH_2, CH_2-CO-, or SO_2;

each of R^6 and R^7, independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkoxy of 3 to 8 carbon atoms, halo, bicycloalkyl of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, 1-indanyloxy, 2-indanyloxy, C_4-C_8-cycloalkylidenemethyl, or C_3-C_{10}-alkylidenemethyl;

each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is

(i) hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino,

alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, halo, or

(ii) one of R^8, R^9, R^{10}, and R^{11} is acylamino comprising a lower alkyl, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen, or

(iii) hydrogen if R^8 and R^9 taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(iv) hydrogen if R^{10} and R^{11}, taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(v) hydrogen if R^9 and R^{10} taken together are benzo; and

(b) The acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

The present invention also pertains to the physiologically acceptable non-toxic acid addition salts of the compound of Formula I. Such salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial

routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds of Formulas I or the compounds of the product in Reaction a associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to

provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

TNFα inhibition in LPS stimulated human peripheral blood mononuclear cells (PBMCs) can be performed as described below. Enzyme-linked immunosorbent assays (ELISA) for TNFα can be performed in a conventional manner. PBMCs are isolated from normal donors by Ficoll-Hypaque density centrifugation. Cells are cultured in RPMI supplemented with 10% AB+ serum, 2mM L-glutamine, 100 U/mL (units per milliliter) penicillin, and 100 mg/mL streptomycin. Drugs are dissolved in dimethylsulfoxide (Sigma Chemical) and further dilutions are done in supplemented RPMI (a well known media). The final dimethylsulfoxide concentration in the presence or absence of drug in the PBMC suspensions is 0.25 wt %. Drugs are assayed at half-log or log dilutions starting at 100 μM. Drugs are added to PBMC (10^6 cells/mL) in 96 wells plates one hour before the addition of LPS. PBMCs (10^6 cells/mL) in the presence or absence of drug are stimulated by treatment with 1 μg/mL or 100 ng/mL of LPS from *Salmonella minnesota* R595 (List Biological Labs, Campbell, CA). Cells are then incubated at 37° C for 18-20 hours. Supernatants are harvested and assayed immediately for TNFα levels or kept frozen at -70°C (for not more than 4 days) until assayed. The concentration of TNFα in the supernatant is determined by human TNFα ELISA kits (ENDOGEN, Boston, MA) according to the manufacturer's directions.

Inhibition of phosphodiesterase type 4 (PDE 4) can also be determined in conventional models. For example, using a modification of the method of Hill and Mitchell, U937 cells (a human promonocytic cell line) are grown to $1x10^6$ cells /mL and collected by centrifugation. A cell pellet of $1x10^9$ cells is washed in phosphate buffered saline and then frozen at -70°C for later purification or immediately lysed in cold homogenization buffer (20mM Tris-HCl, pH 7.1, 3 mM 2-mercaptoethanol, 1 mM

magnesium chloride, 0.1 mM ethylene glycol-*bis*-(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), 1 μM phenylmethylsulfonyl fluoride (PMSF), and 1 μg/mL leupeptin). Cells are homogenized with 20 strokes in a Dounce homogenizer and the supernatant containing the cytosolic fraction are obtained by centrifugation. The supernatant is then loaded onto a Sephacryl S-200 column equilibrated in homogenization buffer. The crude phosphodiesterase type 4 enzyme is eluted in homogenization buffer at a rate of approximately 0.5 mL/min and fractions are assayed for phosphodiesterase activity using rolipram. Fractions containing PDE 4 activity (rolipram sensitive) are pooled and aliquoted for later use.

The phosphodiesterase assay is carried out based on the procedure described by Hill and Mitchell [Hill and Mitchell, *Faseb J.*, 8, A217 (1994)]. The assay is carried out in a total volume of 100 μl containing various concentration of the compounds of interest, 50mM Tris-HCl, pH 7.5, 5 mM magnesium chloride and 1 μM cAMP of which 1% is ^{3}H cAMP. Reactions are incubated at 30 ^{o}C for 30 minutes and then terminated by boiling for 2 minutes. The amount of PDE 4 containing extract used for these experiments is predetermined such that reactions are within the linear range and consume less than 15% of the total substrate. Following termination of reaction, samples are chilled at 4 ^{o}C and then treated with 10μL of 10 mg/mL snake venom for 15 min at 30 ^{o}C. Unused substrate then is removed by adding 200μl of a quaternary ammonium ion exchange resin (AG1-X8, BioRad) for 15 minutes. Samples then are spun at 3000 rpm, 5 min and 50 μl of the aqueous phase are taken for counting. Each data point is carried out in duplicate and activity is expressed as percentage of control. The IC_{50}s of the compounds are then determined from dose response curves of a minimum of three independent experiments.

Representative examples include a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, where the isomer is (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)-pentanoate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoyl-amino) benzoate; (3-(3-cyclopentyloxy-4-methoxy phenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate; (3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate; (3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoyl amino) acetate; (3-(3-ethoxy-4-methoxy-phenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-(3-cyclo-pentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; -N-acetyl-3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; N-acetyl-3-(3-cyclopentyloxy-4-methoxy-phenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-[5-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-ethoxyphenyl)propanoylamino) acetate; (3-(1,3-dioxobenzo[e] isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoyl-amino) acetate; (3-(3-ethoxy-4-methoxyphenyl)-3-phthalimido-propanoyl-amino) pyridine-3-carboxylate; (3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate; (N-acetyl-3-[4-(acetyl-amino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl) propanoyl-amino) acetate; or (3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoyl-amino) acetate. The following examples will serve to further typify the nature of this

invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate

A mixture of 3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanehydroxamic acid (5.8g, 15 mmol) and propionic anhydride (3.93 g, 30.2 mmol) in anhydrous acetonitrile (170 mL) was stirred at room temperature under nitrogen overnight. Removal of solvent in vacuo yielded an oil. The oil was then stirred in ether (25 mL). The resulting suspension was filtered and washed with ether to give (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate as a white solid (2.8 g, 42%): mp, 181.0-183.5 °C; ^{1}H NMR (DMSO-d6) δ 1.01 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.31 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 2.39 (q, J = 7.4 Hz, 2H, CH_2), 3.12-3.35 (m, 2H, CH_2), 3.97 (q, J = 7.4 Hz, 2H, CH_2), 5.67 (t, J = 7.7 Hz, 1H, CH), 6.90 (s, 2H, Ar), 7.02 (s, 1H, Ar), 7.83-7.86 (m, 4H, Ar), 11.87 (br s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 8.2, 14.1, 23.7, 33.4, 49.3, 54.9, 63.2, 111.3, 111.7, 118.9, 122.6, 130.5, 130.7, 134.6, 147.2, 148.1, 166.1, 167.1, 171.1; Anal. Calcd. For $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.62; H, 5.50; N, 6.18.

Example 2

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(1,3-dioxoisoindolin-2-

yl)-3-(3-ethoxy-4-methoxyphenyl)propanehydroxamic acid (0.5 g, 1.3 mmol) and acetic anhydride (0.27 g, 2.6 mmol) in anhydrous acetonitrile (20 mL). The product was obtained as a white solid (0.25 g, 45%): mp, 180.0-182.0 °C; ^{1}H NMR (DMSO-d6) δ 1.31 (t, *J* = 6.7 Hz, 3H, C*H*$_3$), 2.07 (s, 3H, C*H*$_3$), 3.10-3.26 (m, 2H, C*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 4.00 (q, *J* = 6.4 Hz, 2H, OC*H*$_2$), 5.67 (t, *J* = 7.7 Hz, 1H, C*H*), 6.89 (s, 2H, Ar), 7.02 (s, 1H, Ar), 7.82-7.85 (m, 4H, Ar), 11.86 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.6, 17.9, 33.9, 49.8, 55.4, 63.7, 111.8, 112.1, 119.4, 123.1, 130.9, 131.2, 134.5, 147.7, 148.5, 166.5, 167.6, 168.1; Anal. Calcd. For $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.20; N, 6.57. Found: C, 62.01; H, 5.26; N, 6.43.

Example 3

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) pentanoate

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) pentanoate was prepared as described in Example 1 from 3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanehydroxamic acid (1.0 g, 2.6 mmol) and pentanoic anhydride (0.97 g, 5.2 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (0.45 g, 37%): mp, 200.0-201.5 °C; ^{1}H NMR (DMSO-d6) δ 0.83 (t, *J* = 7.3 Hz, 3H, C*H*$_3$), 1.25-1.33 (m, 2H, C*H*$_2$), 1.31 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.33-1.48 (m, 2H, C*H*$_2$), 2.36 (t, *J* = 7.2 Hz, 2H, C*H*$_3$), 3.10-3.20 (m, 2H, C*H*$_2$), 3.72 (s, 3H, C*H*$_3$), 4.02 (q, *J* = 6.4 Hz, 2H, OC*H*$_2$), 5.67 (t, *J* = 7.6 Hz, 1H, C*H*), 6.89-7.01 (m, 3H, Ar), 7.85 (s, 4H, Ar), 11.86 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 13.4, 14.6, 21.3, 26.3, 30.4, 49.7, 55.4, 63.7, 111.8, 112.2, 119.4, 123.1, 130.9, 131.2, 134.5, 147.7, 148.5, 166.6, 167.6, 170.8; Anal. Calcd. for $C_{25}H_{28}N_2O_7$: C, 64.09; H, 6.02; N, 5.98. Found: C, 63.89; H, 6.04; N, 5.81.

Example 4

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) benzoate

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) benzoate was prepared as described in Example 1 from 3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanehydroxamic acid (1.0 g, 2.6 mmol) and phenylcarbonyl benzoate (1.18 g, 5.2 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (0.70 g, 55.1%): mp, 196.0-198.0 °C; ^{1}H NMR (DMSO-d6) δ 1.33 (t, J = 6.6 Hz, 3H, CH_3), 3.31-3.46 (m, 2H, CH_2), 3.74 (s, 3H, OCH_3), 4.03 (q, J = 6.4 Hz, 2H, OCH_2), 5.72 (t, J = 7.5 Hz, 1H, CH), 6.94-7.07 (m, 3H, Ar), 7.50-8.00 (m, 9H, Ar), 12.20 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 55.5, 63.7, 111.8, 112.2, 119.4, 123.2, 126.6, 129.0, 129.4, 131.0, 131.2, 134.3, 134.6, 147.7, 148.6, 163.8, 167.0, 167.6; Anal. Calcd. for $C_{27}H_{24}N_2O_7$: C, 65.42; H, 5.10; N, 5.61. Found: C, 65.10; H, 4.90; N, 5.49.

Example 5

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate was prepared by the general procedure A from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanehydroxamic acid (2.86 g, 7.0 mmol) and acetic anhydride (1.42 g, 14.0 mmol) in anhydrous acetonitrile (110 mL). The product was obtained as a white solid (0.79 g, 27%): mp, 166.0-168.5 °C; ^{1}H NMR (DMSO-d6) δ 1.50-1.82 (m, 8H, C_5H_8), 2.09 (s, 3H, CH_3), 3.04 (d, J = 7.9 Hz, 2H,

CH_2), 3.71 (s, 3H, OCH_3), 4.17 (d, J = 17.4 Hz, 1H, CH*H*),), 4.60 (d, J = 17.4 Hz, 1H, CH*H*), 4.69-4.75 (m, 1H, OC*H*), 5.67 (t, J = 7.8 Hz, 1H, C*H*), 6.83-6.93 (m, 3H, Ar), 7.45-7.70 (m, 4H, Ar), 11.86 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 17.9, 23.5, 32.1, 34.6, 51.0, 55.5, 79.5, 112.2, 113.9, 119.1, 122.8, 123.4, 127.8, 131.3, 131.6, 132.2, 141.7, 146.9, 149.1, 166.6, 167.0, 168.3; Anal. Calcd. for $C_{25}H_{28}N_2O_6$: C, 65.06; H, 6.33; N, 6.07. Found: C, 65.3; H, 6.26; N, 5.85.

Example 6

(3-[4-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate

(3-[4-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate was prepared by the procedure of Example 1 from N-[2-[2-(N-hydroxycarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)ethyl]-1,3-dioxoisoindolin-4-yl]acetamide (0.8 g, 1.8 mmol) and acetic anhydride(0.37 g, 3.6 mmol) in anhydrous acetonitrile (30 mL). The product was isolated as a white solid (0.55 g, 62.8%): mp, 279.0-280.0 °C; ^{1}H NMR (DMSO-d6) δ 1.31 (t, J = 6.9 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.15-3.26 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.97 (q, J = 6.4 Hz, 2H, OCH_2), 5.64 (t, J = 7.7 Hz, 1H, C*H*), 6.90-6.99 (m, 3H, Ar), 7.56 (d, J = 7.3 Hz, 1H, Ar), 7.78 (t, J = 7.7 Hz, 1H, Ar), 8.45 (d, J = 8.0 Hz, 1H, Ar), 9.71 (s, 1H, N*H*), 11.86 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 14.7, 17,9, 24.2, 33.8, 49.7, 55.5, 63.8, 11.8, 118.0, 119.4, 135.8, 136.4, 147.8, 166.6, 167.2, 168.2, 169.3; Anal. Calcd. for $C_{24}H_{25}N_3O_8$: C59.62; H, 5.21; N, 8.69. Found: C, 59.44; H, 5.08; N, 8.50.

Example 7

(3-(3-Ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl) propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanehydroxamic acid (1.0 g, 2.6 mmol) and acetic anhydride(0.53 g, 5.2 mmol) in anhydrous acetonitrile (30 mL). The product was isolated as a white solid (0.5 g, 53.2 %): mp, 124.0-126.0 °C; ^{1}H NMR (DMSO-d6) δ 1.31 (t, J = 6.8 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.15-3.35 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.00 (q, J = 6.4 Hz, 2H, OCH_2), 5.65 (t, J = 7.7 Hz, 1H, NCH), 6.85-7.02 (m, 3H, Ar), 7.61-7.70 (m, 3H, Ar), 11.85 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 14.6, 16.9, 17.9, 33.8, 49.6, 55.4, 63.7, 111.8, 112.2, 119.4, 120.7, 127.8, 131.1, 131.6, 134,0, 136.6, 137.3, 147.7, 148.5, 166.6, 167.5, 168.1, 168.2; Anal. Calcd. for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.49; N, 6.36. Found: C, 62.79; H, 5.35; N, 6.26.

Example 8

(3-(3-Ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl) propanoylamino) acetate was prepared analogously to Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanehydroxamic acid (0.90 g, 2.4 mmol) and acetic anhydride (0.48 g, 4.7 mmol) in anhydrous acetonitrile (27 mL). The product was obtained as a white solid (0.30 g, 30.0 %): mp, 145.0-147.0 °C; ^{1}H NMR (DMSO-d6) δ 1.31 (t, J = 6.9 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.48 (s,

3H, CH_3), 3.20-3.36 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.00 (q, J = 6.4 Hz, 2H, OCH_2), 5.65 (t, J = 7.2 Hz, 1H, CH), 6.89-7.00 (m, 3H, Ar), 7.62-7.76 (m, 3H, Ar), 11.84 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 14.6, 17.9,21.3, 33.9, 49.7, 55.4, 63.7, 111.8, 112.1, 119.3, 128.6, 131.1, 131.6, 134.9, 145.5, 147.7, 148.5, 166.6, 167.6, 167.7, 168.1; Anal. Calcd. for $C_{23}H_{24}N_2O_7$: C, 61.50; H, 5.36; N, 6.07. Found: C, 61.52; H, 5.46; N, 6.21.

Example 9

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate was prepared analogously to Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl) propanehydroxamic acid (1.5 g, 3.4 mmol) and acetic anhydride (0.7 g, 6.8 mmol) in anhydrous acetonitrile (45 mL). The product was obtained as a white solid (0.61 g, 43.3 %): mp, 150.0-152.0 °C; ^1H NMR (DMSO-d6) δ 1.55-1.89 (m, 8H, C_5H_8), 2.08 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.22-3.36 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.50-4.74 (m, 1H, OCH), 5.65 (t, J = 7.5 Hz, 1H, CH), 6.89-7.02 (m, 3H, Ar), 7.58-7.70 (m, 3H, Ar), 11.86 (s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 17.0, 17.9, 23.5, 32.1, 33.9, 49.6, 55.5, 79.6, 112.1, 114.0, 119.4, 120.7, 127.8, 131.1, 131.6, 134.0, 136.6, 137.3, 146.7, 149.2, 166.6, 167.5, 168.1, 168.3; Anal. Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.25; H, 5.82; N, 5.75. Found: C, 64.13; H, 5.72; N, 5.55.

Example 10

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanehydroxamic acid (1.0 g, 2.3 mmol) and acetic anhydride(0.47 g, 4.6 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (0.53 g, 48.5 %): mp, 98.0-101.0 °C; ^{1}H NMR (DMSO-d6) δ 1.50-1.95 (m, 8H, C_5H_8), 2.07 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.10-3.26 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 4.60-4.80 (m, 1H, OC*H*), 5.64 (t, J = 7.7 Hz, 1H, C*H*), 6.88-7.01 (m, 3H, Ar), 7.61-7.76 (m, 3H, Ar), 11.86 (s, 1H, N*H*); ^{13}C NMR (DMSO-d6) δ 17.9, 21.3, 23.5, 32.1, 33.9, 49.8, 55.5, 79.5, 112.1, 113.9, 119.4, 123.0, 123.5, 128.6, 131.0, 131.6, 134.9, 145.5, 146.7, 149.1, 166.6, 167.6, 167.7, 168.1; Anal. Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.68; H, 5.90; N, 5.80. Found: C, 64.47; H, 5.81; N, 5.62.

Example 11

(N-Acetyl-3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(N-Acetyl-3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanehydroxamic acid (0.9 g, 2.3 mmol) and acetic anhydride (0.48 g, 4.7 mmol) in anhydrous

acetonitrile (27 mL). The product was obtained as a white solid (0.06 g, 6 %): mp, 128.0-129.5 °C; ^{1}H NMR (DMSO-d6) δ 1.30 (t, J = 6.8 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.55-4.15 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.00 (q, J = 6.8 Hz, 2H, OCH_2), 5.67 (t, J = 3.3 Hz, 1H, CH), 6.89-7.00 (m, 3H, Ar), 7.62-7.76 (m, 3H, Ar); ^{13}C NMR (DMSO-d6) δ 14.6, 17.9, 21.3, 33.9, 49.7, 55.4, 63.7, 111.8, 112.1, 119.3, 128.6, 131.1, 131.6, 134.9, 145.5, 147.7, 148.5, 166.6, 167.6, 167.7, 168.1; Anal. Calcd. for $C_{25}H_{26}N_2O_8$: C, 62.23; H, 5.43; N, 5.81. Found: C, 61.83; H, 5.33; N, 5.53.

Example 12

(N-Acetyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate

(N-Acetyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxo-isoindolin-2-yl) propanehydroxamic acid (1.5 g, 3.4 mmol) and acetic anhydride (0.7 g, 6.8 mmol) in anhydrous acetonitrile (45 mL). The product was obtained as a white solid (0.21 g, 12.8 %): mp, 120.0-122.0 °C; ^{1}H NMR (DMSO-d6) δ 1.50-1.90 (m, 8H, C_5H_8), 2.28 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.50-4.10 (m, 2H, CH_2), 4.60-4.70 (m, 1H, OCH), 5.67 (t, J = 8.9 Hz, 1H, CH), 6.80-7.10 (m, 3H, Ar), 7.50-7.75 (m, 3H, Ar); ^{13}C NMR (DMSO-d6) δ 17.0, 17.7, 23.5, 23.6, 23.7, 32.1, 49.0, 55.5, 79.6, 112.2, 113.9, 119.3, 120.8, 127.6, 131.1, 131.5, 134.2, 136.8, 137.4, 146.8, 149.2, 167.6, 167.7, 168.3; Anal. Calcd. for $C_{28}H_{30}N_2O_8$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.40; H, 5.73; N, 5.04.

Example 13

(3-[5-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate

(3-[5-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate was prepared by the procedure of Example 1 from N-[2-[2-(N-hydroxycarbamoyl)-1-(3-ethoxy-4-methoxyphenyl)ethyl]-1,3-dioxoisoindolin-5-yl]acetamide (0.75 g, 1.7 mmol) and acetic anhydride (0.21 g, 2.0 mmol) in anhydrous acetonitrile (28 mL). The product was obtained as a white solid (0.60 g, 73 %): mp, 178 °C (decomp.); ^{1}H NMR (DMSO-d6) δ 1.31 (t, J = 7.0 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.19 (dd, J = 7.1, 15 Hz, 1H, CHH), 3.23-3.43 (m, 1H, CHH), 3.72 (s, 3H, CH_3), 3.98 (q, J = 7.0 Hz, 2H, CH_2), 5.63 (t, J = 8.5 Hz, 1H, CH), 6.89 (s, 2H, Ar), 7.00 (s, 1H, Ar), 7.77-7.86 (m, 2H, Ar), 8.17 (d, J = 1.1 Hz, 1H, Ar), 10.56 (br s, 1H, NH), 11.85 (br s, 1H, NH); ^{13}C NMR (DMSO-d6) δ 14.6, 17.9, 24.2, 33.9, 49.8, 55.4, 63.7, 111.7, 112.1, 112.6, 119.3, 123.2, 124.3, 124.8, 131.1, 132.7, 144.8, 147.7, 148.5, 166.5, 167.2, 167.4, 168.1, 169.3; Anal. Calcd. for $C_{24}H_{25}N_3O_8$: C, 59.62; H, 5.21; N, 8.69. Found: C, 59.34; H, 5.30; N, 8.58.

Example 14

(3-(1,3-Dioxobenzo[e]isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate

(3-(1,3-Dioxobenzo[e]isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(1,3-dioxobenzo[e]isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanehydroxamic acid (1.0 g, 2.3 mmol), acetic anhydride (0.50 mL, 5.3 mmol) in acetonitrile (30 mL). The product was obtained as a yellow solid (135 mg, 12% yield): mp, 180 °C (decomp);

^1H NMR (DMSO-d_6) δ 1.30 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 2.04 (s, 3H, C*H*$_3$), 3.24 (dd, *J* = 7.0, 15.1 Hz, 1H, CH*H*), 3.40 (dd, *J* = 8.8, 15.1 Hz, 1H, CH*H*), 3.71 (s, 3H, C*H*$_3$), 4.09 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 5.72 (t, *J* = 8.3 Hz, 1H, NC*H*), 6.89-6.99 (m, 2H, Ar), 7.06 (s, 1H, Ar), 7.72-7.89 (m, 3H, Ar), 8.17 (d, *J* = 8 Hz, 1H, Ar), 8.40 (d, *J* = 8.3 Hz, 1H, Ar), 8.79 (d, *J* = 8.2 Hz, 1H, Ar), 11.90 (brs, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 14.65, 17.87, 34.07, 43.73, 55.43, 63.71, 111.78, 112.20, 118.37, 119.38, 123.80, 126.22, 127.09, 128.79, 129.12, 129.81, 130.74, 131.11, 135.43, 136.16, 147.22, 148.52, 166.58, 168.05, 168.81; Anal Calcd for $C_{26}H_{24}N_2O_7$: C, 65.54; H, 5.08; N, 5.88. Found: C, 65.40; H, 5.27; N, 5.76.

Example 15

(3-(3-Ethoxy-4-methoxyphenyl)-3-phthalimido-propanoylamino) pyridine-3-carboxylate

(3-(3-Ethoxy-4-methoxyphenyl)-3-phthalimido-propanoylamino) pyridine-3-carboxylate was prepared analogously to Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-phthalimido-*N*-hydroxypropionamide (768 mg, 2.0 mmol), triethyl amine (0.7 mL, 5.0 mmol) and nicotinoyl chloride hydrochloride (391 mg, 2.2 mmol) in anhydrous acetonitrile (30 mL). The product was isolated as a white solid (250 mg, 26% yield): mp, 156.0-158.0 °C; ^1H NMR (DMSO-d_6) δ 1.32 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 3.28-3.45 (m, 2H, C*H*$_2$), 3.73 (s, 3H, C*H*$_3$), 4.00 (q, *J* = 6.9 Hz, 2H, C*H*$_2$), 5.71 (t, *J* = 7.5 Hz, 1H, NC*H*), 6.92-6.93 (m, 2H, Ar), 7.05 (br s, 1H, Ar), 7.59 (dd, *J* = 4.8, 7.9 Hz, 1H, Ar), 7.82-7.90 (m, 4H, Ar), 8.28-8.32 (m, 1H, Ar), 8.86-8.88 (m, 1H, Ar), 9.06-9.07 (m, 1H, Ar), 12.32 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 14.66, 33.87, 49.77, 55.45, 63.74, 111.83, 112.24, 119.45, 122.96, 123.17, 124.16, 130.97, 131.22, 134.60, 137.17, 147.75, 148.63, 149.97, 154.56, 162.92, 167.04, 167.64;

Anal Calcd for $C_{26}H_{23}N_3O_7$ + 0.17 H_2O: C, 63.40; H, 4.78; N, 8.53; H_2O, 0.62. Found: C, 63.05; H, 4.64; N, 8.20; H_2O, 0.62.

Example 16

(3-[4-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate

(3-[4-(Acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate was prepared by the procedure of Example 1 from N-[2-[2-(N-hydroxycarbamoyl)-1-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]-1,3-dioxoisoindolin-4-yl]acetamide (1.3 g, 2.7 mmol), acetic anhydride (0.51 mL, 5.4 mmol) in acetonitrile (45 mL). The product was obtained as a yellow solid (95 mg, 7% yield): mp, 97.0-99.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.55-1.85 (m, 8H, C_5H_8), 2.07 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.18-3.37 (m, 2H, CH_2), 4.74 (m, 1H, OC*H*), 5.64 (t, *J* = 7.7 Hz, 1H, NC*H*), 6.91 (br s, 2H, Ar), 7.00 (s, 1H, Ar), 7.56 (d, *J* = 7.2 Hz, 1H, Ar), 7.77 (t, *J* = 8.0 Hz, 1H, Ar), 8.40-8.47 (m, 1H, Ar), 9.71 (br s, 1H, N*H*, Ar), 11.86 (brs, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 17.9, 23.5, 24.2, 32.1, 33.8, 49.7, 55.5, 79.6, 112.1, 114.0, 116.2, 117.9, 119.4, 125.8, 130.8, 131.4, 135.8, 136.1, 146.7, 149.2, 166.5, 167.1, 168.1, 169.2; Anal Calcd for $C_{27}H_{29}N_3O_8$: C, 61.94; H, 5.58; N, 8.03. Found: C, 61.59; H, 5,48; N, 7.88.

Example 17

(N-Acetyl-3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate

(N-Acetyl-3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate was prepared by the procedure of Example 1 from N-[2-[2-(N-hydroxycarbamoyl)-1-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]-

1,3-dioxoisoindolin-4-yl]acetamide (1.3 g, 2.7 mmol), acetic anhydride (0.51 mL, 5.4 mmol) in acetonitrile (45 mL). The product was obtained as a yellow solid (240 mg, 33% yield): mp, 93.0-95.0 °C; ^{1}H NMR (DMSO-d_6) δ 1.55-1.85 (m, 8H, C_5H_8), 2.19 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.55-4.25 (m, 2H, CH_2), 4.74 (m, 1H, OC*H*), 5.68 (dd, *J* = 2.8, 7.7 Hz, 1H, NC*H*), 6.91 (br s, 2H, Ar), 7.00 (s, 1H, Ar), 7.54-7.57 (m, 1H, Ar), 7.78 (t, *J* = 7.6 Hz, 1H, Ar), 8.42-8.47 (m, 1H, Ar), 9.71 (br s, 2H, N*H*, Ar); ^{13}C NMR (DMSO-d_6) δ 17.8, 23.6, 24.4, 32.0, 32.1, 49.0, 55.6, 79.6, 112.1, 114.2, 116.5, 117.6, 118.1, 126.0, 130.8, 131.3, 135.8, 136.3, 146.8, 149.2, 167.1, 167.6, 168.1, 168.5, 169.1, 169.2; Anal Calcd for $C_{29}H_{31}N_3O_9$: C, 61.59; H, 5.52; N, 7.43. Found: C, 61.59; H, 5,46; N, 7.46.

Example 18

(3-(3-Ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate

(3-(3-Ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanehydroxamic acid (500 mg, 1.35 mmol) and acetic anhydride (0.26 mL, 1.8 mmol) in anhydrous acetonitrile (20 mL). The product was obtained as a white solid (480 mg, 86%): mp, 131.5-134.0 °C; ^{1}H NMR (DMSO-d_6); δ 1.29 (t, *J* = 6.9 Hz, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.04 (d, *J* = 7.8 Hz, 2H, CH_2), 3.73 (s, 3H, CH_3), 3.97-4.04 (m, 2H, CH_2), 4.14 (d, *J* = 17.5 Hz, 1H, NCH*H*), 4.58 (d, *J* = 17.5 Hz, 1H, NCH*H*), 5.73 (t, *J* = 7.8 Hz, 1H, NC*H*), 6.85-6.95 (m, 3H, Ar), 7.44-7.70 (m, 4H, Ar), 11.85 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6) δ 14.64, 17.89, 34.62, 46.37, 51.02, 55.43, 63.73, 111.86, 112.13, 119.14, 122.79, 123.36, 127.79, 131.29, 131.59,

132.17, 141.70, 147.88, 148.46, 166.58, 166.89, 168.30; Anal Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.96; H, 5.87; N, 6.58.

Example 19

Tablets, each containing 50 mg of (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate are prepared in the following manner:

<u>Constituents</u> (for 1000 tablets)

(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	50.0 g
lactose	50.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talc	5.0 g
magnesium stearate	1.8 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 20

Tablets, each containing 100 mg of (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate can be prepared in the following manner:

Constituents (for 1000 tablets)	
(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	100.0 g
lactose	100.0 g
wheat starch	47.0 g
magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 21

Tablets for chewing, each containing 75 mg of (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate can be prepared in the following manner:

Composition (for 1000 tablets)

(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	75.0 g
mannitol	230.0 g
lactose	150.0 g
talc	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharin	1.5 g
5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

Example 22

Tablets, each containing 10 mg (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate can be prepared in the following manner:

Composition (for 1000 tablets)

(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	10.0 g
lactose	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 23

Gelatin dry-filled capsules, each containing 100 mg of (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate can be prepared in the following manner:

Composition (for 1000 capsules)

(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	100.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is sieved into the (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

Example 24

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

(3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) propanoate	5.0 g
sodium chloride	22.5 g
phosphate buffer pH 7.4	300.0 g
demineralized water to	2,500.0 mL

(3-(1,3-Dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To

prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

Example 25

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)propanate

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanoylamino)propanate was prepared by the procedure used for example 1 from 3-(4-acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propane-hydroxamic acid (1g, 2.26 mmol) and propionic anhydride (0.59g, 4.53 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (0.96g, 87%): mp, 147-149 °C; ^1H NMR (DMSO-d_6) δ 11.86 (s, 1H), 9.70 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.00-6.91 (m, 3H), 5.65 (t, J = 7.5 Hz, 1H), 4.01 (q, J = 6.9 Hz, 2H), 3.72 (s, 3H), 3.34-3.24 (m, 2H), 2.38 (q, J = 7.5 Hz, 2H), 2.19 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.63, 169.19, 168.15, 167.09, 166.59, 148.61, 147.74, 136.40, 138.73, 131.41, 130.80, 125.75, 119.38, 117.95, 116.62, 112.24, 111.79, 63.77, 55.45, 49.62, 33.75, 24.25, 24.19, 14.66.8.68; Anal. Calcd. For $C_{25}H_{27}N_3O_8$: C, 60.36; H, 5.47; N, 8.45. Found: C, 60.26; H, 5.45; N, 8.39.

Example 26

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)butanoate

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanoylamino)butanoate was prepared by the procedure used for example 1 from 3-(4-acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanehydroxamic acid (1.0 g, 2.26 mmol) and butyric anhydride (0.72 g, 4.53 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (0.93 g, 80%): mp, 105-107 °C; ^1H NMR (DMSO-d_6) δ 11.84 (s, 1H), 9.69 (s, 1H),

8.42 (d, J = 7.5 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 6.99-6.91 (m, 3H), 5.64 (t, J = 7.5 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.31-3.24 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 2.18 (s, 3H), 1.51 (q, J = 7.3 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 170.95, 169.18, 168.09, 166.60, 148.60, 147.73, 136.40, 135.74, 131.42, 130.80, 125.75, 119.36, 117.96, 116.63, 112.22, 111.79, 63.70, 55.46, 49.61, 33.79, 32.56, 24.19, 17.80, 14.66, 13.14; Anal. Calcd. For $C_{28}H_{29}N_3O_8$: C, 61.05: H, 5.71; N, 8.21. Found: C, 60.95; H, 5.73; N, 7.97.

Example 27

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)benzoate

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanoylamino)benzoate was prepared by the procedure used for example 1 from 3-(4-acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propane-hydroxamic acid (1.0g, 2.26 mmol) and benzoic anhydride (1.02g, 4.52 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (1.05g, 55%): mp, 150-152 ^0C; ^1H NMR (DMSO-d_6) δ 12.19 (s, 1H), 9.71 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.96-7.52 (m, 7H), 7.04-6.91 (m, 3H), 5.70 (t, J = 7.5 Hz, 1H), 4.03 (q, J = 6.9 Hz, 2H), 3.74 (s, 3H), 3.44-3.28 (m, 2H), 2.19 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 169.20, 168.17, 167.13, 166.93, 163.87, 148.62, 147.75, 136.42, 135.76, 134.31, 131.44, 130.79, 129.38, 129.05, 126.60, 125.80, 119.39, 118.00, 116.67, 112.24, 111.81, 63.77, 55.47, 49.60, 33.77, 24.20, 14.67; Anal. Calcd. For $C_{29}H_{27}N_3O_8$: C, 63.85; H, 4.99; N, 7.70. Found: C, 63.86; H, 4.98; N, 7.45.

Example 28

(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino)isobutanoate

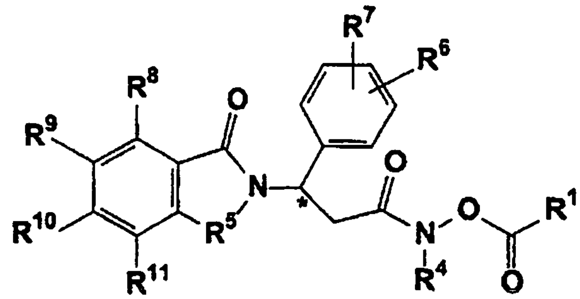
(3-(4-Acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanoylamino)isobutanoate was prepared by the procedure used for example 1

from 3-(4-acetylamino-1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)-propanehydroxamic acid (1.0g, 2.26 mmol) and isobutyric anhydride (0.72g, 4.52 mmol) in anhydrous acetonitrile (30 mL). The product was obtained as a white solid (1.02g, 87%): mp, 104-106 °C; ^1H NMR (DMSO-d_6) δ 11.84 (s, 1H), 9.70 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 6.99-6.91 (m, 3H), 5.64 (t, J = 7.5 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.33-3.25 (m, 2H), 2.68-2.62 (m, 1H), 2.19 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.15-1.04 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 174.10, 169.18, 168.11, 167.06, 166.66, 148.60, 147.72, 136.40, 135.73, 131.40, 130.80, 125.77, 119.36, 117.96, 116.62, 112.24, 111.79, 63.75, 55.45, 49.54, 33.78, 31.20, 24.17, 18.58, 14.54; Anal. Calcd. For $C_{26}H_{29}N_3O_8$: C, 61.05; H, 5.71; N, 8.21. Found: C, 60.97; H, 5.83; N, 7.96.

We claim:

1. An acylhydroxamic acid derivative selected from the group consisting of

(a) compounds of the formula:



wherein

the carbon atom designated * constitutes a center of chirality,

R^4 is hydrogen or –(C=O)–R^{12};

each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl methyl, pyridyl, imidazoyl, imidazolyl methyl, or $CHR^*(CH_2)_nNR^*R^0$

wherein $R^*$and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and n = 0, 1, 2;

R^5 is C=O, CH_2, CH_2-CO-, or SO_2;

each of R^6 and R^7, independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkoxy of 3 to 8 carbon atoms, halo, bicycloalkyl of up to 18 carbon atoms, tricycloalkoxy of up to 18 carbon atoms, 1-indanyloxy, 2-indanyloxy, C_4-C_8-cycloalkylidenemethyl, or C_3-C_{10}-alkylidenemethyl;

each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is

(i) hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, halo, or

(ii) one of R^8, R^9, R^{10}, and R^{11} is acylamino comprising a lower alkyl, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen, or

(iii) hydrogen if R^8 and R^9 taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(iv) hydrogen if R^{10} and R^{11}, taken together are benzo, quinoline, quinoxaline, benzimidazole, benzodioxole, 2-hydroxybenzimidazole, methylenedioxy, dialkoxy, or dialkyl, or

(v) hydrogen if R^9 and R^{10} taken together are benzo; and

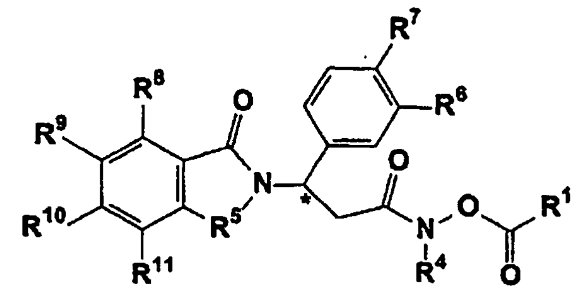
(b) The acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

2. An acylhydroxamic acid derivative according to claim 1 wherein each of R^8, R^9, R^{10}, and R^{11} is hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms.

3. An acylhydroxamic acid derivative according to claim 1 wherein one of R^8, R^9, R^{10}, and R^{11} is amino, alkyl amino, dialkyl amino, or acyl amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or hydroxy, and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen.

4. An acylhydroxamic acid derivative according to claim 1 wherein R^8, R^9, R^{10}, and R^{11} are hydrogen.

5. An acylhydroxamic acid derivative according to claim 1 wherein said compound has the formula:



in which

the carbon atom designated * constitutes a center of chirality;

R^4 is hydrogen or $-(C{=}O)-R^{12}$, where

each of R^1 and R^{12}, independently of each other, is alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridyl, pyridyl methyl, imidazolyl, imidazoylmethyl, or $CHR^*(CH_2)_nNR^*R^0$

wherein R^* and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and n = 0, 1, 2;

R^5 is C=O or CH_2;

each of R^6 and R^7, independently of the other is alkoxy of 1 to 8 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms; C_4-C_6-cycloalkylidenemethyl, C_2-C_{10}-alkylidenemethyl, C_6-C_{18}-bicycloalkoxy, C_6-C_{18}-tricycloalkoxy, 1-indanyloxy, or 2-indanyloxy; and

each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, halo, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, and alkoxy of 1 to 10 carbon atoms

6. An acylhydroxamic acid derivative according to claim 5, wherein each of R^8, R^9, R^{10}, and R^{11}, independently of the others, is hydrogen, alkyl of 1 to 4 carbon atoms, halo, or alkoxy of 1 to 4 carbon atoms.

7. An acylhydroxamic acid derivative according to claim 5 wherein one of R^8, R^9, R^{10}, and R^{11} is acylamino, amino, hydroxy, alkyl of 1 to 10 carbon atoms, and the remaining of R^8, R^9, R^{10}, and R^{11}, are hydrogen.

8. An acylhydroxamic acid derivative according to claim 5, wherein R^8, R^9, R^{10}, and R^{11} are
   (a) at least one alkyl of 1 to 10 carbon atoms with the remainder of R^8, R^9, R^{10}, and R^{11} being hydrogen, or
   (b) at least one alkoxy of 1 to 10 carbon atoms with the remainder of R^8, R^9, R^{10}, and R^{11} being hydrogen.

9. An acylhydroxamic acid derivative according to claim 5 wherein R^8, R^9, R^{10}, and R^{11} are hydrogen.

10. An acylhydroxamic acid derivative according to claim 5 wherein one of R^8, R^9, R^{10}, and R^{11} is acylamino and the remaining of R^8, R^9, R^{10}, and R^{11} are hydrogen.

11. An acylhydroxamic acid derivative according to claim 5 wherein two of R^8, R^9, R^{10}, and R^{11} are hydrogen and the remaining of R^8, R^9, R^{10}, and R^{11}, independent of each other, are alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, amino, or acylamino.

12. An acylhydroxamic acid derivative according to claim 5 wherein R^4 is hydrogen.

13. An acylhydroxamic acid derivative according to claim 5 wherein R^4 is $-(C{=}O)-R^{12}$, and where R^{12} is a lower alkyl of 1 to 6 carbon atoms.

14. An acylhydroxamic acid derivative according to claim 5, wherein
R^4 is hydrogen;
R^5 is C=O;
R^8 is hydrogen; and
one of R^9 and R^{11} is hydrogen and the other of R^9 and R^{11}, taken together with R^{10}, is benzo.

15. An acylhydroxamic acid derivative according to claim 5, wherein
R^4 is hydrogen;
R^5 is C=O;
R^8 and R^9 are hydrogen; and
R^{10} and R^{11}, taken together, are methylenedioxo or dialkoxyl.

16. An acylhydroxamic acid derivative according to claim 5, wherein
R^7 is methoxy; and
R^6 is ethoxy, cyclopentoxy, or isopropoxy.

17. An acylhydroxamic acid derivative according to claim 5 wherein R^6 and R^7 are independently of each other, alkoxy or 1 to 10 carbon atoms, cycloalkoxy, or bicycloalkoxy.

18. An acylhydroxamic acid derivative according to claim 1, which is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

19. A pharmaceutical composition comprising a quantity of an acylhydroxamic acid derivative according to claim 1, which derivative is a substantially chirally pure (R) -isomer, a substantially chirally pure (S)-isomer, or a mixture thereof,

sufficient upon administration in a single or multiple dose regimen to reduce or inhibit levels of TNFα or in a mammal in combination with a carrier.

20. A pharmaceutical composition comprising a quantity of an acylhydroxamic acid derivative according to claim 1, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, sufficient upon administration in a single or multiple dose regimen to inhibit undesirable levels of at least one of matrix metalloproteinases and PDE 4 in a mammal in combination with a carrier.

21. A method of inhibiting undesirable levels of TNFα in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 1, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

22. A method of inhibiting undesirable levels of matrix metalloproteinases in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 1, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

23. A method of treating in a mammal a disease selected from the group consisting of inflammatory disease and autoimmune disease, which comprises administering thereto an effective amount of a compound according to claim 1, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

24. A method according to claim 23 wherein the disease is at least one member selected from the group of arthritis, rheumatoid arthritis, inflammatory bowel

disease, Crohn's disease, aphthous ulcers, cachexia, graft versus host disease, asthma, COPD, psoriasis, atopic dermatitis, Lupus, adult respiratory distress syndrome, and acquired immune deficiency syndrome.

25. A method of treating cancer in a mammal which comprises administering thereto an effective amount of a compound according to claim 1, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

26. A method of treating undesirable angiogenesis in a mammal which comprises administering thereto an effective amount of a compound according to claim 1, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

27. A method of inhibiting phosphodiesterases type IV or PDE 4 in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 1, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

28. An acylhydroxamic acid derivative according to claim 1, wherein the compound is selected from the group consisting of a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, where the isomer is (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) propanoate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxy phenyl)propanoylamino) pentanoate; (3-(1,3-dioxoisoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) benzoate; (3-(3-cyclopentyloxy-4-methoxy phenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate; (3-[4-(acetylamino)-1,3-

dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl) propanoylamino) acetate; (3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoyl amino) acetate; (3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; -N-acetyl-3-(3-ethoxy-4-methoxyphenyl)-3-(5-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; N-acetyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(4-methyl-1,3-dioxoisoindolin-2-yl)propanoylamino) acetate; (3-[5-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-ethoxy-4-methoxyphenyl)propanoylamino) acetate; (3-(1,3-dioxobenzo[e] isoindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl) propanoyl-amino) acetate; (3-(3-ethoxy-4-methoxyphenyl)-3-phthalimido-propanoylamino) pyridine-3-carboxylate; (3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoylamino) acetate; (N-acetyl-3-[4-(acetylamino)-1,3-dioxoisoindolin-2-yl]-3-(3-cyclopentyloxy-4-methoxyphenyl) propanoylamino) acetate; or (3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisoindolin-2-yl)propanoylamino) acetate.

29. An acylhydroxamic acid derivative according to claim 5, which is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

30. A pharmaceutical composition comprising a quantity of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, sufficient upon administration in a single or multiple dose regimen to reduce or inhibit levels of TNFα in a mammal in combination with a carrier.

31. A pharmaceutical composition comprising a quantity of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof, sufficient upon administration in a single or multiple dose regimen to inhibit undesirable levels of matrix metalloproteinases or PDE 4 in a mammal in combination with a carrier.

32. A method of reducing or inhibiting undesirable levels of TNFα in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

33. A method of inhibiting undesirable levels of matrix metalloproteinases in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

34. A method of treating in a mammal a disease selected from the group consisting of inflammatory disease and autoimmune disease, which comprises administering thereto an effective amount of a compound according to claim 5, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

35. A method according to claim 34, wherein the disease is at least one member selected from the group consisting of arthritis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, aphthous ulcers, cachexia, graft versus host

disease, asthma, COPD, psoriasis, stopic dermatitis, Lupus, adult respiratory distress syndrome, and acquired immune deficiency syndrome

36. A method of treating cancer in a mammal which comprises administering thereto an effective amount of a compound according to claim 5, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

37. A method of treating undesirable angiogenesis in a mammal which comprises administering thereto an effective amount of a compound according to claim 5, which compound is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

38. A method of inhibiting undesirable levels of phosphodiesterase type IV in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

39. A method of treating dermal diseases in a mammal which comprises administering thereto an effective amount of an acylhydroxamic acid derivative according to claim 5, which derivative is a substantially chirally pure (R)-isomer, a substantially chirally pure (S)-isomer, or a mixture thereof.

40. An acylhydroxamic acid derivative according to claim 10 wherein acyl contains a carbonyl group and alkyl of 1 to 6 carbon atoms, phenyl, benzyl, pyridylmethyl, pyridyl, imidazoyl, imidazolylmethlyl, or $CHR^*(CH_2)_nNR^*R^0$, wherein $R^*$and R^0, independently of the other, are hydrogen, alkyl of 1 to 6 carbon atoms, phenyl,

benzyl, pyridylmethyl, pyridyl, imidazoyl or imidazolylmethlyl, and $n = 0; 1, 2$.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34455

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/40, 31/44; C07D 209/46, 209/48, 209/56, 401/06
US CL : 514/339, 411, 416, 417; 546/277.1; 548/451, 472, 477
According to International Patent Classification (IPC) or to both national classification and IPC
B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/339, 411, 416, 417; 546/277.1; 548/451, 472, 477
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/06041 A1 (CELGENE CORPORATION) 11 February 1999, see entire document.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2001 (13.02.2001)	08 MAR 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Brenda L. Coleman Dolk Collins for Telephone No. 703-308-1235

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